	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2002/10/29 12:02
2	L2	302653	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2002/10/29 12:03
3	L3	63566	promoter$1	USPAT; US-PGPUB	2002/10/29 12:03
4	L4	1256081	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2002/10/29 12:03
5	L5	49	2 near10 4 near10 3	USPAT; US-PGPUB	2002/10/29 12:04
6	L6	7894	pps or phosphoenol adj pyruvate adj synthase1	USPAT; US-PGPUB	2002/10/29 12:06
7	L7	7896	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2002/10/29 12:06
8	L8	75	7 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2002/10/29 12:07
9	L9	15	8 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2002/10/29 12:08
10	L10	13	8 and 2	USPAT; US-PGPUB	2002/10/29 12:16

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2002/10/29 10:56

US-PAT-NO: 6254874

DOCUMENT-IDENTIFIER: US 6254874 B1

TITLE: Attenuated auxotrophic microorganisms having a combination of non-attenuating mutations and method for making same

DATE-ISSUED: July 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mekalanos; John J.	Cambridge	MA	N/A	N/A
Klose; Karl E.	Newton	MA	N/A	N/A

APPL-NO: 08/ 421207

DATE FILED: April 13, 1995

US-CL-CURRENT: 424/234.1; 424/184.1 ; 424/258.1 ; 424/93.2 ; 424/93.4 ; 424/93.48 ; 435/252.33 ; 435/252.8 ; 435/471 ; 435/69.3

ABSTRACT:

A live non-virulent vaccine composition and method for preparing the same comprising a virulent microorganismal strain which contains at least two mutations, wherein the first mutation results in an auxotrophic mutant which requires for proliferation, a nutrient which is normally available in the host tissues in an amount required by the auxotrophic mutant for proliferation and the second mutation results in the inability of the auxotrophic mutant to specifically transport the required nutrient from host-tissues into the auxotrophic mutant thereby producing an attenuated strain.

57 Claims, 4 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

---------- KWIC ---------

Detailed Description Text - DETX:

Glutamine synthetase levels are modulated by controlling the level of transcription of glnA. glnA is a member of the glnA ntrBC operon, shown in FIG. 2, which includes in addition to glnA, two other nitrogen regulatory genes ntrB and ntrC, also referred to as glnL and glnG, respectively. Three promoters exist in the glnA ntrBC operon. **glnAp1,** with a transcriptional startsite located 187 base pairs (bp) upstream from the translational startsite

in glnA; **glnAp2,** with a transcriptional startsite 85 bp upstream from the translational startsite in glnA; and ntrBp, with a transcriptional site located 256 bp downstream from the translational termination site in glnA and 33 bp upstream from the translational startsite in ntrB. Reitzer and Magasanik, Escherichia coli and Salmonella typhimurium, Cellular and Molecular Biology, American Society of Microbiology, pp. 302-320 (1987), herein incorporated by reference.

Detailed Description Text - DETX:

Under conditions of nitrogen excess, both NTRC and NTRB (also referred to as NR.sub.I and NR.sub.II, respectively) the nitrogen regulatory proteins of structural genes ntrC and ntrB, respectively, exist at low levels predominantly in their inactive forms. NTRC is a DNA binding protein that recognizes and binds two adjacent sequences (labeled 1 and 2, in FIG. 2) located within the **glnAp1** promoter and one sequence (labeled 3) located within ntrBp. Transcription of glutamine synthetase, under nitrogen excess conditions, occurs at low levels through activation of **glnAp1** by .sigma..sup.70 RNA polymerase.

Detailed Description Text - DETX:

RNA polymerase or the holoenzyme, as it is commonly referred to, can be separated biochemically into two components, the core enzyme and the sigma factor (the .sigma. polypeptide). The names reflect the fact that only the holoenzyme can initiate transcription; but then the sigma "factor" is released, leaving the core enzyme to undertake elongation. The function of the sigma factor is to ensure that RNA polymerase binds stably to DNA and initiates transcription only at promoters, not at other sites. Sigma factor also confers the ability to recognize specific binding sites and different sigma factors recognize different promoters. Therefore, .sigma..sup.70 is the sigma factor, discussed previously, responsible for recognizing the **glnAp1** promoter and initiating transcription of glutamine synthetase.

Detailed Description Text - DETX:

When nitrogen becomes limiting, NTRB is activated in response to a lower level of internal glutamine such that it causes phosphorylation of NTRC; NTRC-phosphate then acts as a transcriptional activator, activating initiation of transcription at **glnAp2** by .sigma..sup.54 -RNA polymerase (.sigma..sup.54 associated with core RNA polymerase). NTRC phosphate catalyzes the isomerization of the closed .sigma..sup.54 -RNA polymerase promoter complex to an open complex. Consequently, glutamine synthetase expression is initiated at the major glnA promoter, **glnAp2,** resulting in high levels of glutamine synthetase, NTRB and NTRC in order to increase internal glutamine levels. The resulting increase in the level of NTRC furthermore results in the complete repression of transcription initiating at **glnAp1** and ntrBp. As discussed previously, NTRC binding sites exist within **glnAp1** and ntrBp and as a result of the increasing levels of NTRC-phosphate bound at these sites .sigma..sup.70 RNA polymerase is prevented from recognizing and initiating transcription at the

glnApl and ntrBp promoters. Shifting the microorganisms from nitrogen starvation to nitrogen excess causes NTRB to facilitate the removal of phosphate from NTRC-phosphate, bringing an end to the initiation of transcription at **glnAp2**. Continued growth in this nitrogen rich media results in the decline of levels of glutamine synthetase and NTRC by dilution. Consequently, the repression of **glnAp1** and ntrBp by NTRC is lifted sufficiently to allow both glutamine synthetase and NTRC to be maintained at their respective low levels.

Detailed Description Text - DETX:

.sigma..sup.54 (also referred to as .sigma..sup.60, .sigma..sup.N, or NTRA) is encoded by the structural gene ntrA (alternately designated glnF or rpoN) and, as discussed above, is a positive regulatory factor needed for the expression of the gene encoding glutamine synthetase from the major **glnAp2** promoters. .sigma..sup.54, is required for the transcription of the nitrogen fixation (nif) genes in a number of bacteria, and is required for transcription of genes encoding amino acid transport, such as glutamine, degradative enzymes, as well as many other genes. See, Dixon, R., J. Gen. Microbiol., 130:2745-2755 (1984), Magasanik, B., Annu. Rev. Genet., 16:135-168 (1982), and S. Kustu et al., Micro. Biol. Reviews, 53:367-376 (1989).

Detailed Description Text - DETX:

In an alternate embodiment, live vaccines prepared in accordance with the preferred embodiment which have non-reverting mutations in genes under nitrogen control may be used as vectors or carriers for antigens of species other than the non-virulent pathogenic vaccine. One or more structural genes coding for the desired antigens may be operatively linked to an ntr-regulated promoter. As the non-virulent pathogenic microbe senses a nitrogen deficiency, expression of the ntr genes increases accordingly, thus initiating expression of genes transcribed from ntr promoters. For example, one or more structural genes coding for the desired antigens may be operatively linked to the **glnAp2** promoter located on a suicide vector or an autonomously replicating plasmid. The suicide vector or plasmid may then be introduced into the non-virulent pathogenic strain having non-reverting mutations located in the genes glnA and glnH or glnQ, by well known methods, such as, transduction, transformation, electroporation, tri-parental mating techniques or direct transfer of a self mobilized vector in a bi-parental mating and maintained within the microorganism either autonomously or in the bacterial host's chromosomal DNA. Therefore, under low internal glutamine conditions which this attenuated strain must experience, the **glnAp2** promoter will be activated and express the structural genes that have been operatively linked thereto. As discussed, in detail above, activation of an ntr promoter requires the proteins NTRA and NTRC, therefore this alternate embodiment will only work if the ntrA and ntrC genes are fully functional. Thus, this particular embodiment would be based on a strain prepared according to the preferred embodiment of the present invention and not the second embodiment of the present invention.

US-PAT-NO: 6162640

DOCUMENT-IDENTIFIER: US 6162640 A

TITLE: Selection methods

DATE-ISSUED: December 19, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wohlstadter; Jacob Nathaniel	Andover	MA	01810	N/A

APPL-NO: 08/ 447515

DATE FILED: May 23, 1995

PARENT-CASE:

This application is a division of copending U.S. application Ser. No. 08/235,437, filed Apr. 29, 1994, which in turn is a continuation of U.S. application Ser. No. 07/852,412, filed Mar. 16, 1992 and now abandoned.

US-CL-CURRENT: 435/325; 435/243 ; 435/440 ; 435/6

ABSTRACT:

A rational method for obtaining a novel molecule capable of a desired interaction with a substrate of interest comprising selecting hosts or replicators which incode said novel molecules based upon cell or replicator growth caused by the desired interaction of the novel molecule and a selection molecule expressed by said host.

78 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX:

The cells are then incubated in glutamine and nitrogen limiting media. Cells capable of growth are selected. In this example selection occurs through a cascade. A properly phosphorylated NRI is capable of acting as an enhancer to the promoter **glnApZ** recognized by .sigma..sup.54 by binding an upstream DNA sequence. The enhanced **glnApZ** promoter then allows for the high level

expression of glnA (glutamine synthetase) and DNaA. These proteins then in turn activate cascades which allow for cellular growth and replication.

US-PAT-NO: 6087177

DOCUMENT-IDENTIFIER: US 6087177 A

TITLE: Selection methods

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wohlstadter; Jacob Nathaniel	Andover	MA	01810	N/A

APPL-NO: 08/ 235437

DATE FILED: April 29, 1994

PARENT-CASE:

This is a continuation of application Ser. No. 07/852,412, filed Mar. 16, 1992, which is incorporated by reference herein in its entirety now abandoned.

US-CL-CURRENT: 435/440; 435/320.1

ABSTRACT:

A rational method for obtaining a novel molecule capable of a desired interaction with a substrate of interest comprising selecting hosts or replicators which encode said novel molecules based upon cell or replicator growth caused by the desired interaction of the novel molecule and a selection molecule expressed by said host.

66 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX:

The cells are then incubated in glutamine and nitrogen limiting media. Cells capable of growth are selected. In this example selection occurs through a cascade. A properly phosphorylated NR.sub.I is capable of acting as an enhancer to the promoter **glnApZ** recognized by .sigma..sup.54 by binding an upstream DNA sequence. The enhanced **glnApZ** promoter then allows for the high level expression of glnA (glutamine synthetase) and DNaA. These proteins then

in turn active cascades which allow for cellular growth and replication.

US-PAT-NO: 6066499

DOCUMENT-IDENTIFIER: US 6066499 A

TITLE: Selection methods

DATE-ISSUED: May 23, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wohlstadter; Jacob Nathaniel	Andover	MA	01810	N/A

APPL-NO: 08/ 447506

DATE FILED: May 23, 1995

PARENT-CASE:

This application is a division of U.S. application Ser. No. 08/235,437, filed Apr. 29, 1994, which in turn is a continuation of U.S. application Ser. No. 07/852,412, filed Mar. 16, 1992 and now abandoned.

US-CL-CURRENT: 435/325; 435/243 ; 435/440 ; 435/6

ABSTRACT:

A rational method for obtaining a novel molecule capable of a desired interaction with a substrate of interest comprising selecting hosts or replicators which encode said novel molecules based upon cell or replicator growth caused by the desired interaction of the molecule and a selection molecule expressed by said host.

168 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX:

The cells are then incubated in glutamine and nitrogen limiting media. Cells capable of growth are selected. In this example selection occurs through a cascade. A properly phosphorylated NR.sub.I is capable of acting as an enhancer to the promoter **glnApZ** recognized by .sigma..sup.54 by binding an upstream DNA sequence. The enhanced **glnApZ** promoter then allows for the high

level expression of glna (glutamine synthetase) and DNa. These proteins then in turn activate cascades which allow for cellular growth and replication.

US-PAT-NO: 6043093

DOCUMENT-IDENTIFIER: US 6043093 A

TITLE: Selection methods

DATE-ISSUED: March 28, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wohlstadter; Jacob Nathaniel	Andover	MA	01810	N/A

APPL-NO: 08/ 485324

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation of copending U.S. application Ser. No. 08/235,437, filed Apr. 29, 1994, which in turn is a continuation of U.S. application Ser. No. 07/852,412, filed Mar. 16, 1992 and now abandoned.

US-CL-CURRENT: 435/440; 435/243 ; 435/325 ; 435/6

ABSTRACT:

A rational method for obtaining a novel molecule capable of a desired interaction with a substrate of interest comprising selecting hosts or replicators which encode said novel molecules based upon cell or replicator growth caused by the desired interaction of the novel molecule and a selection molecule expressed by said host.

137 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX:

The cells are then incubated in glutamine and nitrogen limiting media. Cells capable of growth are selected. In this example selection occurs through a cascade. A properly phosphorylated NR.sub.I is capable of acting as an enhancer to the promoter **glnApZ** recognized by .sigma..sup.54 by binding an upstream DNA sequence. The enhanced **glnApZ** promoter then allows for the high

level expression of glnA (glutamine synthetase) and DNaA. These proteins then in turn activate cascades which allow for cellular growth and replication.

US-PAT-NO: 4970147

DOCUMENT-IDENTIFIER: US 4970147 A

TITLE: Oxygen regulatable gene expression

DATE-ISSUED: November 13, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huala; Eva	Belmont	MA	N/A	N/A
Gu; Qing	Cambridge	MA	N/A	N/A
Albright; Lisa	Reading	MA	N/A	N/A
Ausubel; Frederick	Newton	MA	N/A	N/A

APPL-NO: 07/ 169488

DATE FILED: March 17, 1988

US-CL-CURRENT: 435/69.1; 435/252.3 ; 435/320.1 ; 435/476 ; 435/488 ; 435/71.1 ; 435/91.41 ; 536/23.2 ; 536/24.1

ABSTRACT:

The invention discloses that, in the presence of NifA and NtrA, the expression of a desired DNA molecule which has been operably linked to an ntrA-RNA polymerase and NifA dependent promoter can be regulated by regulating the oxygen level of the culture medium. The invention relates to vectors which may be used in accordance with this discovery, and to methods for using such vectors.

11 Claims, 4 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

---------- KWIC ---------

Detailed Description Text - DETX:

The requirements for an upstream binding site at a particular promoter in vivo might vary depending upon the NtrA-polymerase, the transcriptional activator and the concentration of the activator. In vivo and in vitro experiments with NtrC show that by increasing its concentration one can compensate for deletion of its binding site upstream of the **glnAP.sub.2** promoter (Austin, S., et al., Mol. Microb. 1:92-100 (1987)).

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2002/10/29 12:02
2	L2	302653	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2002/10/29 12:03
3	L3	63566	promoter$1	USPAT; US-PGPUB	2002/10/29 12:03
4	L4	1256081	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2002/10/29 12:03
5	L5	49	2 near10 4 near10 3	USPAT; US-PGPUB	2002/10/29 12:04

PGPUB-DOCUMENT-NUMBER: 20020137910

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020137910 A1

TITLE: MN gene and protein

PUBLICATION-DATE: September 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Zavada, Jan	Prague		CZ	
Pastorekova, Silvia	Bratislava		SK	
Pastorek, Jaromir	Bratislava		SK	

APPL-NO: 09/ 772719

DATE FILED: January 30, 2001

RELATED-US-APPL-DATA:

child 09772719 A1 20010130 parent continuation-of 08485049 19950607 US PATENTED child 08485049 19950607 US parent continuation-in-part-of 08260190 19940615 US PENDING child 08260190 19940615 US parent continuation-in-part-of 08177093 19931230 US PATENTED child 08177093 19931230 US parent continuation-in-part-of 07964589 19921021 US PATENTED

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
CS	PV-709-92	1992CS-PV-709-92	March 11, 1992

US-CL-CURRENT: 536/23.2,435/6 ,435/7.23 ,530/350

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are effective to immunize a vertebrate against neoplastic diseases associated with the expression of MN proteins. The invention still further concerns antisense

nucleic acid sequences that can be used to inhibit MN gene expression, and polymerase chain reaction (PCR) assays to detect genetic rearrangements.

[0001] This application is a continuation-in-part of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now pending U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995, but from which a now pending continuation U.S. Ser. No. 08/335,469 was filed on Nov. 7, 1994. This application declares priority under 35 USC .sctn.120 from those U.S. applications, and also under 35 USC .sctn.119 from the now pending Czechoslovakian patent application PV-709-92 (filed Mar. 11, 1992).

---------- KWIC ---------

Detail Description Paragraph - DETX:

[0124] No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 6437216

DOCUMENT-IDENTIFIER: US 6437216 B1

TITLE: Transgenic models of inflammatory disease

DATE-ISSUED: August 20, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Duff; Gordon W.	Sheffield	N/A	N/A	GB
Nicklin; Martin	Sheffield	N/A	N/A	GB

APPL-NO: 09/ 647826

DATE FILED: March 12, 2001

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9723835	November 13, 1997

PCT-DATA:
APPL-NO: PCT/US98/24287
DATE-FILED: November 13, 1998
PUB-NO: WO99/25857
PUB-DATE: May 27, 1999
371-DATE: Mar 12, 2001
102(E)-DATE: Mar 12, 2001

US-CL-CURRENT: 800/21; 435/320.1 ; 435/325 ; 536/23.1 ; 800/18 ; 800/3

ABSTRACT:

The present provides a mammal in which the expression of one or more interleukin genes has been suppressed. More specifically, the invention concerns the inactivating deletion of the interleukin-1 receptor antagonist gene to produce a knock-out non-human mammal with decreased or completely suppressed expression of the endogenous gene. The invention provides methods for preparing such knock-out mammals and methods of using the knock-out mammals to evaluate the effectiveness of therapeutic agents and regimens to treat diseases or disorders associated with perturbations in the interleukin pathways.

21 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Detailed Description Text - DETX:

Although the early signals required for IL-1 signal transduction remain under debate, the increased transcription of APR RNAs consequent to IL-I receptor interactions requires the activation of factors that bind to the 5' regulatory regions of the IL-1 responsive genes. The activation of the cytoplasmic transcription factor nuclear factor kappa B (NF.kappa.B) is via the IL-1-induced phosphorylation and dissociation of its associated inhibitor protein I.kappa.B thereby allowing it to enter the nucleus and bind to DNA. NF.kappa.B is centrally involved in the IL-1 directed gene activation of a number of APR genes. Thus IL-1 signaling involves the mobilization of preexisting transcription factors. In addition, the induction of gene expression in IL-1 responsive genes can be achieved with phorbol myristate **acetate (PMA) which activates the transcription factors c-fos/c-jun that bind to AP1 sites in the promoters**. As both PMA and IL-1 can stimulate the synthesis of these DNA binding proteins the capacity of IL-1 to increase the absolute levels of transcription factors represents an additional means of control of gene expression.

US-PAT-NO: 6313373

DOCUMENT-IDENTIFIER: US 6313373 B1

TITLE: Tissue specific promoters and transgenic mouse for the screening of pharmaceuticals

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Eckert; Richard L.	Cleveland Hts.	OH	N/A	N/A
Crish; James F.	North Olmsted	OH	N/A	N/A

APPL-NO: 09/ 430201

DATE FILED: October 29, 1999

PARENT-CASE:

This application for a nonprovisional U.S. Utility Patent Application claims priority to Provisional U.S. patent application Ser. No. 60/106,495 filed on Oct. 30 1998.

US-CL-CURRENT: 800/18; 435/320.1 ; 435/325 ; 435/455 ; 536/23.1 ; 800/10 ; 800/25 ; 800/3

ABSTRACT:

The present invention provides human involucrin (hINV) sequences having tissue specific and cell type specific promoter activity. The sequences provided herein direct expression to suprabasal cells of stratifying epithelia. The invention further provides methods for the production of transgenic animals which contain a hINV promoter sequence which directs the expression of human papillomavirus 16 oncogenes (or other oncogenes). These animals display cervical and epidermal hyperplasias as well as cancer of the trachea, esophagus, colon, epidermis, anus/rectum, lymph nodes, spleen and lung. The animals of the invention provide a useful model for screening potential anti-neoplastic compounds, carcinogens, and co-carcinogens for a number of cancers.

28 Claims, 13 Drawing figures

Exemplary Claim Number: 15,20,21

Number of Drawing Sheets: 15

---------- KWIC ---------

Detailed Description Text - DETX:

DNA sequence analysis indicates that the DRR contains binding sites for several transcription factors, in including functionally important Sp1 and AP1 sites (Welter, et al. "Fos-related antigen (Fra-1), junB, and junD activate human involucrin promoter transcription by binding to proximal and distal AP1 sites to mediate phorbol ester effects on promoter activity" J. Biol. Chem. 270:12614-12622, 1995; Banks, et al. " Characterization of human involucrin promoter distal regulatory region transcriptional activator elements-a role for Sp1 and AP1 binding sites" Biochem. J. 331:61-68, 1998; Efimova, et al. "Regulation of human involucrin promoter activity by a protein kinase C, Ras, MEKK1, MEK3, p38/RK, AP1 signal transduction pathway" J. Biol. Chem. 272:24387-24395, 1998). Our previous in vitro studies show that the basal promoter does not drive expression in karatinocytes; however, addition of the DRR restores hINV promoter activity (Banks, et al. "Characterization of human involucrin promoter distal regulatory region transcriptional activator elements-a role for Sp1 and AP1 binding sites" Biochem. J. 331:61-68, 1998). Moreover, mutation of the AP1 site (AP1-5) inactivates the promoter (see, e.g., Examples 7-9). AP1 has been shown to be an important regulator in several genes that are expressed in a differentiation-dependent manner in surface epithelia (DiSepio, et al. "The proximal promoter of the mouse loricrin gene contains a functional AP1 element and directs keratinocyte-specific but not differentiation-specific expression" J. Biol. Chem. 270:10792-10799, 1995; Takahashi and Iizuka "Analysis of the 5'-upstream **promoter region of human involucrin gene: activation by 12-O-tetradecanoylphorbol-13-acetate**" J. Invest. Dermatol. 100:10-15, 1993). With out limiting the present invention to any mechanism, the present investigation shows that the AP1 site contained within the nucleotide sequence from -2473 to -1953 of FIG. 6 is important in the regulation of expression of the hINV gene as well as any sequences that may be operably linked to said sequence.

US-PAT-NO: 6313165

DOCUMENT-IDENTIFIER: US 6313165 B1

TITLE: Inhibition of cataracts and other disorders

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Grunberger; Dezider	Teaneck	NJ	N/A	N/A
Frenkel; Krystyna	Woodmer	NY	N/A	N/A

APPL-NO: 08/ 704545

DATE FILED: December 23, 1996

PARENT-CASE:

This application is a 321 of PCT/US95/03392 filed Mar. 14, 1995, which is a CIP of Ser. No. 08/212,569 filed Mar. 14, 1994 now is U.S. Pat. No. 5,591,773.

PCT-DATA:
APPL-NO: PCT/US95/03392
DATE-FILED: March 14, 1995
PUB-NO:
PUB-DATE:
371-DATE: Dec 23, 1996
102(E)-DATE: Dec 23, 1996

US-CL-CURRENT: 514/532; 514/544

ABSTRACT:

A method of inhibiting the formation of a cataract in an eye by contacting the eye with a compound having the structure: ##STR1##

is described. Also described is a method of inhibiting the progression of cataract formation in an eye. Methods comprising administering a pharmaceutical composition comprising the above compound to inhibit the formation of a cataract in the eye of a subject and to inhibit progression of cataract formation in the eye of a subject are also described. The above compound also prevents diseases resulting from oxidative stress, including diseases comprising tumor formation resulting from oxidative stress, and also inhibits the progression of diseases resulting from oxidative stress. The above compound may furthermore be used to treat an HIV infection when combined in a pharmaceutical composition with a substance which inhibits HIV replication.

12 Claims, 13 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 13

---------- KWIC ---------

Brief Summary Text - BSTX:

It has recently been shown that the phorbol ester-type tumor **promoters (12-O-tetradecanoylphorbol-13-acetate, hereinafter TPA) induce** H.sub.2 O.sub.2 production in mouse skin as well as cause oxidation of DNA bases in vivo (20-22). In addition, it has been found that agents possessing anti-tumor-promoting properties in vivo, also suppress inflammatory processes. Processes suppressed by such agents include infiltration of polymorphonuclear leukocytes (hereinafter PMNs), reactive oxygen species production, and oxidation of DNA bases (20-22), as well as induction of ornithine decarboxylase (ODC) and edema (23-26). A number of known anti-tumor promoters that possess all or some of those properties have been isolated from biological sources, and include sarcophytol A (isolate from marine soft coral) (27, 28), (-)-epigallocatechin gallate (EGCG, a polyphenol from green tea) (26, 29, 30), curcumin (a spice) (24, 25), and caffeic acid (24, 25).

US-PAT-NO: 6312697

DOCUMENT-IDENTIFIER: US 6312697 B1

TITLE: Inhibitory effect of synthetic and natural colorants on carcinogenesis

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind J.	Potomac	MD	20854	N/A
Tokuda; Harukuni	N/A	N/A	N/A	N/A
N/A	Kyoto 602	N/A	N/A	JP
Konoshima; Takao	N/A	N/A	N/A	N/A
N/A	Kyoto 607	N/A	N/A	JP
Takasaki; Midori	Kyoto 602			JP
Nishino; Hoyoku	Kyoto 602			JP

APPL-NO: 09/ 256206

DATE FILED: February 24, 1999

PARENT-CASE:

This application is a divisional application of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997, which in turn claims the benefit of U.S. Provisional Application No. 60/022,638, filed Jul. 24, 1996. [, and of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997.]

US-CL-CURRENT: 424/757

ABSTRACT:

A method of reducing the percentage of Epstein-Barr virus genome-carrying cells which exhibit Epstein-Barr virus early antigen induction, where the Epstein-Barr virus genone-carrying cells have been cultivated in the presence of at least one tumor-promoting chemical. The method is carried out by cultivating Epstein-Barr virus genome-carrying cells in the presence of a tumor-promoting chemical; and treating the Epstein-Barr virus genome-carrying cells with betanins. The betanins are effectively reduce the incidence of Epstein-Barr virus early antigen induction in the cultivated Epstein-Barr virus genome-carrying cells.

4 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter 12O-tetradecanoylphorbol13-acetate** (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lympholastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6291215

DOCUMENT-IDENTIFIER: US 6291215 B1

TITLE: Inhibitory effects on synthetic and natural colorants on carcinogenes

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind J.	Potomac	MD	20854	N/A
Tokuda; Harukuni	N/A	N/A	N/A	N/A
N/A	Kyoto	N/A	N/A	JP
Konoshima; Takao	N/A	N/A	N/A	N/A
N/A	Kyoto	N/A	N/A	JP
Takasaki; Midori	Kyoto			JP
Nishino; Hoyoku	Kyoto			JP

APPL-NO: 09/ 256205

DATE FILED: February 24, 1999

PARENT-CASE:

This application is a divisional application of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997, now U.S. Pat. No. 5,935,581 which in turn claims the benefti of U.S. Provisional Application No. 60/022,638, filed Jul. 24, 1996.

US-CL-CURRENT: 435/125; 435/88

ABSTRACT:

A method of reducing the percentage of Epstein-Barr virus genome-carrying cells which exhibit Epstein-Barr virus early antigen induction, where the Epstein-Barr virus genome-carrying cells have been cultivated in the presence of at least one tumor-promoting or tumor-inducing chemical. The method is carried out by cultivating Epstein-Barr virus genome-carrying cells in the presence of a tumor-promoting or tumor-inducing chemical; and treating the Epstein-Barr virus genome-carrying cells with a synthetic fluorescein dye. The dyes effectively reduce the incidence of Epstein-Barr virus early antigen induction in the cultivated Epstein-Barr virus genome-carrying cells.

11 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate** (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lymphoblastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6284224

DOCUMENT-IDENTIFIER: US 6284224 B1

TITLE: Inhibitory effect of synthetic and natural colorants on carcinogenesis

DATE-ISSUED: September 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind J.	Potomac	MD	20854	N/A
Tokoda; Harunkuni	N/A	N/A	N/A	N/A
N/A	Kyoto 602	N/A	N/A	JP
Konoshima; Takao	N/A	N/A	N/A	N/A
N/A	Kyoto 607	N/A	N/A	JP
Takasaki; Midori	Kyoto 602			JP
Nishino; Hoyoku	Kyoto 602			JP

APPL-NO: 09/ 256201

DATE FILED: February 24, 1999

PARENT-CASE:

This application is a divisional application of U.S. application No. 08/845,166, filed Apr. 21, 1997 now U.S. Pat. No. 5,935,581 which in turn claims the benefit of U.S. Provisional Application No. 60/022,638, filed Jul. 24, 1996.

US-CL-CURRENT: 424/9.8; 424/9.1 ; 424/9.6

ABSTRACT:

A method of treating a group of mammals which have been topically exposed to a tumor promoter or a tumor initiator so as to reduce the percentage of mammals which exhibit formation of epidermal tumors. The topically exposed tissue is treated with an acetone solution containing a defined amount of a synthetic colorant. Preferably, the synthetic colorant is tartrazine or erythrosine B.

10 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate** (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lymphoblastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6277378

DOCUMENT-IDENTIFIER: US 6277378 B1

TITLE: Inhibitory effect of synthetic and natural colorants on carcinogenesis

DATE-ISSUED: August 21, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind J.	Potomac	MD	20854	N/A
Tokuda; Harukuni	N/A	N/A	N/A	N/A
N/A	Kyoto 602	N/A	N/A	JP
Konoshima; Takao	N/A	N/A	N/A	N/A
N/A	Kyoto 607	N/A	N/A	JP
Takasaki; Midori	Kyoto 602			JP
Nishino; Hoyoku	Kyoto 602			JP

APPL-NO: 09/ 256200

DATE FILED: February 24, 1999

PARENT-CASE:

This application is a divisional application of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997, now U.S. Pat. No. 5,935,581, which claims the benefit of provisional application No. 60/022,638, filed Jul. 24, 1996.

US-CL-CURRENT: 424/760; 424/776

ABSTRACT:

A method of preventing inflammation of epidermal tissue resulting from exposure to a chemical by topically applying an acetone solution containing a natural colorant to the exposed tissue. The natural colorant is preferably a paprika extract containing a mixture of capsanthin, capsorubin, and their acyl esters, or an annatto seed extract containing a mixture of cis-bixin, trans-bixin, and cis-norbixin.

2 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate** (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lymphoblastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6267946

DOCUMENT-IDENTIFIER: US 6267946 B1

TITLE: Inhibitory effects of synthetic and natural colorants on carcinogenesis VI

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind	Potomac	MD	20854	N/A

APPL-NO: 09/ 256204

DATE FILED: February 24, 1999

PARENT-CASE:

This application is a divisional application of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997, which in turn claims the benefit of U.S. Provisional Application No. 60/022,638, filed Jul. 24, 1996.

US-CL-CURRENT: 424/9.1; 514/658 ; 514/679

ABSTRACT:

A method of reducing the percentage of Epstein-Barr virus genome-carrying cells which exhibit Epstein-Barr virus early antigen induction, wherein the Epstein-Barr virus genome-carrying cells have been cultivated in the presence of a tumor-promoting chemical and/or a tumor-inducing chemical. The method is performed by:

a) cultivating Epstein-Barr virus genome-carrying cells in the presence of a tumor-promoting chemical and/or a tumor-inducing chemical; and

b) treating the Epstein-Barr virus genome-carrying cells with a synthetic anthraquinone colorant containing a sulfonated phenylamino group. The colorant is effective to reduce the incidence of Epstein-Barr virus early antigen induction in the cultivated Epstein-Barr virus genome-carrying cells.

19 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate** (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lymphoblastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6225296

DOCUMENT-IDENTIFIER: US 6225296 B1

TITLE: Inhibitory effects of synthetic and natural colorant on carcinogenesis VIII

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind	Potomac	MD	20854	N/A

APPL-NO: 09/ 256202

DATE FILED: February 24, 1999

PARENT-CASE:

This application claims the benefit of U.S. Provisional Application No. 60/022,638, filed Jul. 24, 1996, and of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997.

US-CL-CURRENT: 514/150; 424/9.1 ; 514/166

ABSTRACT:

A method of inhibiting Epstein-Barr virus early antigen induction in Epstein-Barr virus genome-carrying cells which have been cultivated in vitro in a medium containing at least one chemical selected from the group consisting of tumor-inducing chemicals and tumor promoting chemicals by adding an effective amount of a synthetic colorant to the medium, wherein the synthetic colorant is an aromatic azo dye.

23 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter**

12-O-tetradecanoylphorbol-13-acetate (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lymphoblastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6204370

DOCUMENT-IDENTIFIER: US 6204370 B1

TITLE: MN gene and protein

DATE-ISSUED: March 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CZ
Pastorekova; Silvia	Bratislava	N/A	N/A	CZ
Pastorek; Jaromir	Bratislava	N/A	N/A	CZ

APPL-NO: 08/ 485049

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation-in-part of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now pending U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995, but from which a now pending continuation U.S. Ser. No. 08/335,469 was filed on Nov. 7, 1994.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CZ	709-92	March 11, 1992

US-CL-CURRENT: 536/23.1; 435/6 ; 536/24.3

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are effective to immunize a vertebrate against neoplastic diseases associated with the expression of MN proteins. The invention still further concerns antisense nucleic acid sequences that can be used to inhibit MN gene expression, and

polymerase chain reaction (PCR) assays to detect genetic rearrangements.

57 Claims, 41 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 6203839

DOCUMENT-IDENTIFIER: US 6203839 B1

TITLE: Flavorant compositions

DATE-ISSUED: March 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bachmann; Jean-Pierre	Wadenswil	N/A	N/A	CH
Gautschi; Markus	Zeiningen	N/A	N/A	CH
Hostettler; Bernhard	Gockhausen	N/A	N/A	CH
Yang; Xiaogen	West Chester	OH	N/A	N/A

APPL-NO: 09/ 212985

DATE FILED: December 16, 1998

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
EP	97122633	December 22, 1997

US-CL-CURRENT: 426/546; 426/538 ; 426/638 ; 426/650

ABSTRACT:

The invention is related to a flavorant composition containing 1'-acetoxychavicol acetate and 1'-acetoxyeugenol acetate derivatives thereof as well as a flavorant acceptable carrier. The flavorant composition may be used for flavoring foods, beverages or healthcare products with warm/hot, spicy and pungent sensations related to Galangal.

2 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Other Reference Publication - OREF:

Kondo et al., 1'Acetoxychavicol **Acetate as a Potent Inhibitor of Tumor Promoter-induced** Epstein-Barr Virus Activation from Languas galanga, a Traditional Thai Condiment, Biosci. Biotech. Biochem. 57(8) (1993) 1344-1345.

US-PAT-NO: 6200760

DOCUMENT-IDENTIFIER: US 6200760 B1

TITLE: Method of screening agents as candidates for drugs or sources of drugs

DATE-ISSUED: March 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dannenberg; Andrew J.	New York	NY	N/A	N/A
Subbaramaiah; Kotha J.	Flushing	NY	N/A	N/A
Pasco; David S.	Oxford	MS	N/A	N/A

APPL-NO: 09/ 355940

DATE FILED: August 13, 1999

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS This application is the national phase of PCT/US98100023, filed Jan. 12, 1998, which claims the benefit of U.S. Provisional Application No. 60/038,254, filed Feb. 24, 1997.

PCT-DATA:
APPL-NO: PCT/US98/00023
DATE-FILED: January 12, 1998
PUB-NO: WO98/37235
PUB-DATE: Aug 27, 1998
371-DATE: Aug 13, 1999
102(E)-DATE: Aug 13, 1999

US-CL-CURRENT: 435/6; 435/4 ; 435/471 ; 435/476 ; 435/8 ; 435/91.1

ABSTRACT:

Cells are transfected with a construct containing transcriptional promoter element(s) that have been implicated in carcinogenesis or inflammation ligated to a reporter gene. Determination of inhibition of activation of said promoter element(s) by putative agent indicates the agent is a candidate as a drug or source of a drug for prophylaxis or treatment of cancer or inflammation. The method has particular application to screening agents as candidates for drugs or sources of drugs for prophylaxis or treatment of human disorders caused or mediated by cyclooxygenase-2 and/or matrix metalloproteinases.

2 Claims, 12 Drawing figures

Exemplary Claim Number: 2

Number of Drawing Sheets: 6

---------- KWIC ---------

Detailed Description Text - DETX:

The activator can be any substance which is known to stimulate transcription. Such **activators include, for example, tumor promoters such as phorbol esters (e.g., phorbol myristate acetate,** e.g., phorbol 12-myristate 13-acetate), serum (e.g., fetal bovine serum), cytokines (e.g., tumor necrosis factor or interleukin-1), growth factors (e.g., epidermal growth factor which may be referred to as EGF), benzo[a]pyrene, lipopolysaccharide, bile acids (e.g., chenodeoxycholate and deoxycholate), free radical producing compounds such as hydrogen peroxide and cyclic AMP generating agents such as forskolin. The particular activators utilized will depend on the transcriptional promoter element in the construct. For the broad and medium cyclooxygenase-2 promoter regions (-1475/+59, -1432/+59, -375/+59, and -327/+59), phorbol esters and epidermal growth factor are useful as activators. For cyclic AMP response elements, cyclic AMP generating agents are useful as activators. For NF-.kappa.B elements, free radical producing agents, phorbol esters and cytokines are useful activators. For the Ets2AP-1 promoter, phorbol esters are useful as activators.

Detailed Description Text - DETX:

In a very preferred method herein for screening for candidates for treatment of an inflammatory and/or carcinogenic disorder, the cells that are transfected are chondrocytes and a battery of screenings are carried out on each putative compound, where in one case the chondrocytes are transfected with a construct containing the COX-2 **promoter and the activator is phorbol myristate acetate** used in combination with interleukin-1; in another case, the chondrocytes are transfected with Ets2/AP-1 transcription **promoter elements and the activator used is phorbol myristate acetate; in another case, the chondrocytes are transfected with construct containing NF-.kappa.B transcription promoter** element (a synthetic element containing the NF-.kappa.B motif from HIV/IgK) and the activator is interleukin-1; in another case, the chondrocytes are transfected with construct containing said NF-.kappa.B transcription promoter element and the activator is tumor necrosis factor-alpha; and in another case, the chondrocytes are transfected with construct containing said NF-.kappa.B transcription **promoter element and the activator is phorbol myristate acetate**. The more cases of inhibition of activation, the higher the likelihood of antiinflammatory and therefore anticancer property.

Detailed Description Text - DETX:

The following combinations of construct in transfected cells and inducer were utilized: (1) COX-2 **promoter ligated to luciferase as construct and phorbol myristate acetate together with interleukin-1 as inducer; (2) Ets2/AP-1 ligated to luciferase as construct and phorbol myristate acetate as inducer**; (3)

NF-.kappa.B ligated to luciferase as construct and interleukin-1 as inducer; (4) NF-.kappa.B ligated to luciferase as construct and tumor necrosis factor-alpha as inducer; (5) NF-.kappa.B ligated to luciferase as construct and phorbol myristate acetate as inducer; and (6) Sp1-luciferase as construct and phorbol myristate acetate together with interleukin-1 inducer.

US-PAT-NO: 6103933

DOCUMENT-IDENTIFIER: US 6103933 A

TITLE: Methods for controlling the oxidation rate of a hydrocarbon by adjusting the ratio of the hydrocarbon to a rate-modulator

DATE-ISSUED: August 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
DeCoster; David C.	Buckley	WA	N/A	N/A
Rostami; Ader M.	Bainbridge Island	WA	N/A	N/A
Dassel; Mark W.	Indianola	WA	N/A	N/A
Vassiliou; Eustathios	Newark	DE	N/A	N/A

APPL-NO: 08/ 861180

DATE FILED: May 21, 1997

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS This application claims priority from U.S. Provisional Application No. 60/030,699 filed Nov. 7, 1996, which application is incorporated herein by reference in its entirety.

US-CL-CURRENT: 562/509

ABSTRACT:

Methods for controlling the oxidation rate of a hydrocarbon to an acid by adjusting addition of a rate-modulator are disclosed. In order to control oxidation rate, the ratio of hydrocarbon to rate modulator is appropriately adjusted. Preferably, this ratio is adjusted continually based on feedback relative to oxidation progress parameters. It may be kept substantially constant at steady state conditions of the oxidation, or it may take a path of predetermined values. The rate-modulator preferably comprises a hydrocarbon oxidation initiator.

91 Claims, 3 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 3

---------- KWIC ---------

Detailed Description Text - DETX:

In operation of this embodiment, hydrocarbon, cyclohexane for example, solvent, acetic acid for example, catalyst, cobalt **acetate tetrahydrate for example, preferably in the form of a solution comprising solvent for example, and a rate modulator, such as an oxidation initiator or promoter,** like cyclohexanone or acetaldehyde, for example enter the major reaction chamber 12 as disclosed in our our co-pending applications, and/or patents. At the same time that the aforementioned ingredients enter the major reaction chamber 12, a gaseous oxidant also enters through line 18, and starts reacting with the hydrocarbon. No recyclables exist at the initial stages.

US-PAT-NO: 6093548

DOCUMENT-IDENTIFIER: US 6093548 A

TITLE: Detection and quantitation of MN-specific antibodies.

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CZ
Pastorekova; Silvia	Bratislava	N/A	N/A	SK
Pastorek; Jaromir	Bratislava	N/A	N/A	SK

APPL-NO: 08/ 485863

DATE FILED: June 7, 1995

PARENT-CASE:

This is a continuation-in-part of now U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now allowed U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995 a continuation of which was filed on Nov. 21, 1999 as U.S. Pat. no. 6,004,535.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CZ	709-92	March 11, 1992

US-CL-CURRENT: 435/7.1; 424/147.1 ; 424/159.1 ; 424/183.1 ; 435/7.21 ; 530/300 ; 530/350 ; 530/387.1 ; 530/388.8

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN

antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are effective to immunize a

vertebrate against neoplastic diseases associated with the expression of MN proteins. The invention still further concerns antisense nucleic acid sequences that can be used to inhibit MN gene expression, and polymerase chain reaction (PCR) assays to detect genetic rearrangements.

21 Claims, 59 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 6080411

DOCUMENT-IDENTIFIER: US 6080411 A

TITLE: Inhibitory effects of synthetic and natural colorants on carcinogenesis III

DATE-ISSUED: June 27, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kapadia; Govind	Potomac	MD	20854	N/A

APPL-NO: 09/ 256199

DATE FILED: February 24, 1999

PARENT-CASE:

This application claims the benefit of U.S. Provisional Application No. 60/022,638, filed Jul. 24, 1996, and of U.S. application Ser. No. 08/845,166, filed Apr. 21, 1997, now U.S. Pat. No. 5,935,581.

US-CL-CURRENT: 424/760

ABSTRACT:

A method of reducing the incidence of splenomegalia induced by ultra violet radiation in mammals by exposing a group of test mammals to intense ultraviolet radiation, where the exposure is repeated at regular intervals over a test period such that the cumulative radiation exposure per mammal is sufficient to cause an increase in an average spleen size in a group of unprotected mammals; and administering drinking water containing a defined concentration of betanins to the group of test mammals during the test period, said defined concentration being sufficient to prevent such an increase in average spleen size.

7 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

A first object of this invention is to evaluate a series of FDA-approved synthetic food colorants for inhibitory effects on carcinogenesis. The

colorants were tested using in vitro assays for inhibition of Epstein-Barr virus early antigen (EBV-EA) **induction in cells exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate** (TPA). High inhibitory activity toward EBV-EA induction is known to be indicative that a composition has potential utility as an anti-tumor promoting or cancer chemopreventive agent. Epstein-Barr virus genome-carrying lymphoblastoid cells (Raji cells) were used in the in vitro studies.

US-PAT-NO: 6074979

DOCUMENT-IDENTIFIER: US 6074979 A

TITLE: Polybetaine-stabilized, palladium-containing nanoparticles, a process for preparing them and also catalysts prepared from them for producing vinyl acetate

DATE-ISSUED: June 13, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hagemeyer; Alfred	Frankfurt	N/A	N/A	DE
Dingerdissen; Uwe	Seeheim-Jugenheim	N/A	N/A	DE
Millauer; Hans	Eschborn	N/A	N/A	DE
Manz; Andreas	Sinzheim	N/A	N/A	DE
Kuhlein; Klaus	Kelkheim	N/A	N/A	DE

APPL-NO: 09/ 083008

DATE FILED: May 21, 1998

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
DE	197 21 601	May 23, 1997

US-CL-CURRENT: 502/159; 502/326 ; 502/330 ; 502/339

ABSTRACT:

Polybetaine-stabilized, palladium-containing nanoparticles, a process for preparing them and also catalysts prepared from them for producing vinyl acetate. The invention relates to soluble nanoparticles which comprise palladium alone or palladium together with metals of the groups 8-11 of the periodic table and which are embedded in protective colloids, wherein the protective colloids comprise at least one polymer having betaine groups, and to a process for preparing them. The soluble nanoparticles are suitable for the preparation of catalysts.

32 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX:

The carrier can also be loaded with further **activators, especially alkali metal**

acetates, preferably potassium acetate and, where appropriate, promoters, for example Zr, Ti, Cd, Cu, Ba and Re compounds, before, during and/or after the immobilization of the sols.

US-PAT-NO: 6069242

DOCUMENT-IDENTIFIER: US 6069242 A

TITLE: MN gene and protein

DATE-ISSUED: May 30, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CS
Pastorekova; Silvia	Bratislava	N/A	N/A	SK
Pastorek; Jaromir	Bratislava	N/A	N/A	SK

APPL-NO: 08/ 487077

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation-in-part of U.S. Ser. No. 08/335,469 filed Nov. 7, 1994 now U.S. Pat. No. 6,004,535 and a c-i-p of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now allowed U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), now U.S. Pat. No. 6,051,226, which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995. This application declares priority under 35 USC .sctn. 120 from those U.S. applications, and also under 35 USC .sctn. 119 from the now pending Czechoslovakian patent application PV-709-92 (filed Mar. 11, 1992).

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CZ	709-92	March 11, 1992

US-CL-CURRENT: 536/24.31; 435/320.1 ; 435/375 ; 435/6 ; 536/23.1 ; 536/24.3 ; 536/24.5

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic

acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are effective to immunize a vertebrate against neoplastic diseases associated with the expression of MN proteins. The invention still further concerns antisense nucleic acid sequences that can be used to inhibit MN gene expression, and polymerase chain reaction (PCR) assays to detect genetic rearrangements.

10 Claims, 43 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 6066488

DOCUMENT-IDENTIFIER: US 6066488 A

TITLE: Cathepsin C homolog

DATE-ISSUED: May 23, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Coleman; Roger	Mountain View	CA	N/A	N/A
Braxton; Scott Michael	San Mateo	CA	N/A	N/A
Seilhamer; Jeffrey J.	Los Altos Hills	CA	N/A	N/A

APPL-NO: 08/ 871314

DATE FILED: June 9, 1997

PARENT-CASE:

The present U.S. utility patent application is a divisional application of then U.S. Ser. No. 08/426,428, filed Apr. 19, 1995, now U.S. Pat. No. 5,637,462, from which priority is claimed.

US-CL-CURRENT: 435/212; 424/94.63 ; 424/94.65 ; 435/219 ; 435/226 ; 435/320.1 ; 435/325 ; 530/412 ; 536/23.1 ; 536/23.2

ABSTRACT:

The present invention provides nucleotide and amino acid sequences that identify and encode a new cathepsin C homolog (RCP) expressed in THP-1 cells. The present invention also provides for antisense molecules to the nucleotide sequences which encode RCP, expression vectors for the production of purified RCP, antibodies capable of binding specifically to RCP, hybridization probes or oligonucleotides for the detection of RCP-encoding nucleotide sequences, genetically engineered host cells for the expression of RCP, diagnostic tests for activation of monocyte/macrophages based on RCP-encoding nucleic acid molecules, and use of the protein to produce antibodies capable of binding specifically to the protein and use of the protein to screen for inhibitors.

4 Claims, 3 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

Many human myeloid and myelomonocytic cell lines retain some ability to differentiate into more mature phenotypes in response to various internal stimuli including growth factors, lymphokines, cytokines, vitamin D derivatives, and tumor promoters and external agents such as trauma, smoking, UV irradiation, asbestos exposure, and steroids. THP-1 cells treated with the tumor **promoter 12-O-tetradecanoyl-phorbol-13 acetate (TPA) are induced** to stop proliferating and differentiate into macrophage-like cells which mimic native monocyte-derived macrophages both morphologically and physiologically.

US-PAT-NO: 6057346

DOCUMENT-IDENTIFIER: US 6057346 A

TITLE: Inhibition of retroviral LTR promoters by calcium response modifiers

DATE-ISSUED: May 2, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kohn; Elise C.	Olney	MD	N/A	N/A
Liotta; Lance A.	Potomac	MD	N/A	N/A
Gardner; Kevin L.	Gaithersburg	MD	N/A	N/A

APPL-NO: 08/ 353765

DATE FILED: December 12, 1994

US-CL-CURRENT: 514/359; 514/252.1 ; 514/255.05 ; 514/256 ; 514/259.31 ; 514/263.2 ; 514/383 ; 514/396 ; 514/398 ; 514/399 ; 514/407

ABSTRACT:

A class of calcium-response modification compounds is disclosed which inhibits the activation of retroviral LTR promoters, including the HIV-LTR. This class of compounds are used to delay or suppress the transition of a retroviral infection from a latent to a virulent condition, thereby ameliorating retrovirally caused diseases such as AIDS. The compounds are also useful in cancer treatment, allowing for coordinated therapeutic approaches to retroviral diseases and related cancers such as AIDS and Kaposi's Sarcoma. The compounds are also useful in standardizing in vitro assays of clinical and experimental importance.

21 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Brief Summary Text - BSTX:

The present invention demonstrates that CAI inhibits **activation of the HIV LTR promoter by the phorbol ester 12-myristic 13-acetate** (PMA) and the mitogenic lectin phytohemagglutinin (PHA). Thus, the inhibition of the HIV LTR which is provided by CAI is more general than that provided by cyclosporin A, and in all likelihood represents inhibition of the signal transduction events leading to

LTR activation at a different point in the regulatory cascade than cyclosporin A. This discovery provides for the use of calcium-flux modulators as AIDS therapeutics, as well as for a variety of improvements to in vitro manipulations of HIV-infected cells. These calcium-flux modulators can be compounds which are structurally related to CAI, and which are known to have similar biological properties, such as those described in co-pending application Ser. No. 08/209,089, or they can be chemically unrelated compounds that are known to have similar biological properties. For instance, Compound 2 (below) is not closely related to CAI structurally, but it is known to have comparable effects on receptor-operated calcium influx (See, Gusovsky, et al., J. Biol. Chem. 268:7768-7772 (1993) and Merritt, et al., J. Biol. Chem 271:515-522 (1990)), and can be used to inhibit the HIV-LTR. ##STR2##

US-PAT-NO: 5998188

DOCUMENT-IDENTIFIER: US 5998188 A

TITLE: Mitogen activated protein kinase phosphatase cDNAS and their biologically active expression products

DATE-ISSUED: December 7, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stork; Philip J. S.	Portland	OR	N/A	N/A
Misra-Press; Anita	Portland	OR	N/A	N/A

APPL-NO: 08/ 990379

DATE FILED: December 15, 1997

PARENT-CASE:

RELATED APPLICATIONS The present application claims priority under 35 U.S.C. .sctn.120 from PCT International Application No. PCT/US96/10402, filed Jun. 14, 1996, which is a continuation of U.S. Provisional Ser. No. 60/000,263, filed Jun. 16, 1995, all hereby expressly incorporated by reference.

US-CL-CURRENT: 435/196

ABSTRACT:

The invention relates to a novel mitogen-activated protein kinase phosphatase, MKP-2. The invention further relates to methods and means for preparing and to nucleic acids encoding this protein. The MKP-2 of the present invention is useful in the control of cell growth, differentiation and apoptosis.

3 Claims, 44 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 24

---------- KWIC ---------

Detailed Description Text - DETX:

ERK activity is reduced in MKP-1 and MKP-2 overexpressing cells. Growth factor, hormone, and phorbol ester stimulation of PC12 cells has been known to activate the MAP kinase pathway and to stimulate the enzymatic activity of

ERK-1 (FIGS. 13A and 13B) (61, 62, 65, 69, 71). We compared the enzymatic activity of ERK-1, in wild type cells and in MKP overexpressing cells treated with these agents. PC12 cells treated for 10 minutes with mitogenic agents such as EGF, differentiating agents such as NGF and forskolin, and the tumor **promoter phorbol 12-myristate 132-acetate (PMA), produce a robust activation** of ERK-1 as measured by an immune complex activity assay (FIG. 13A). MKP-1 and MKP-2 overexpressing clones were then treated with the same agents for the identical times. Both MKP1.10 and MKP2.3 cells lines showed a dramatic reduction in the ability of growth factors and hormones to activate ERK-1 (FIG. 13A). Additional positive clones were also analyzed and showed similar results (data not shown). Quantitation of the immune complex assays shows that the modest overexpression of MKP-1 and MKP-2 mRNA in PC12 cells inhibited growth factor and hormoneinduced activation of ERKs 80-90% in MKP2.3 cells and 50-80% in MKP1.0 cells compared to the fold activation seen.in wild type PC12 cells (FIG. 13B). The basal ERK activity also appeared to be lower in these MKP overexpression cells as compared to wild type cells (FIG. 13B), insert).

US-PAT-NO: 5989838

DOCUMENT-IDENTIFIER: US 5989838 A

TITLE: Immunological methods of detecting MN proteins and MN polypeptides

DATE-ISSUED: November 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CZ
Pastorekova; Silvia	Bratislava	N/A	N/A	SK
Pastorek; Jaromir	Bratislava	N/A	N/A	SK

APPL-NO: 08/ 485862

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation-in-part of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now pending U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995. This application declares priority under 35 USC .sctn. 120 from those U.S. applications, and also under 35 USC .sctn. 119 from the now pending Czechoslovakian patent application PV-709-92 (filed Mar. 11, 1992).

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CS	709-92	March 11, 1992

US-CL-CURRENT: 435/7.23; 530/387.7 ; 530/388.8 ; 530/389.7

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are effective to immunize a vertebrate against neoplastic diseases associated with

the expression of MN proteins. The invention still further concerns antisense nucleic acid sequences that can be used to inhibit MN gene expression, and polymerase chain reaction (PCR) assays to detect genetic rearrangements.

37 Claims, 58 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 5981711

DOCUMENT-IDENTIFIER: US 5981711 A

TITLE: MN-specific antibodies and hybridomas

DATE-ISSUED: November 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CZ
Pastorekova; Silvia	Bratislava	N/A	N/A	SK
Pastorek; Jaromir	Bratislava	N/A	N/A	SK

APPL-NO: 08/ 486756

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation-in-part of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now pending U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995. This application declares priority under 35 USC .sctn. 120 from those U.S. applications, and also under 35 USC .sctn. 119 from the now pending Czechoslovakian patent application PV-709-92 (filed Mar. 11, 1992).

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CZ	709-92	March 11, 1992

US-CL-CURRENT: 530/387.7; 424/138.1 ; 424/155.1 ; 424/174.1 ; 435/330 ; 435/344 ; 530/388.8 ; 530/389.7

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are

effective to immunize a vertebrate against neoplastic diseases associated with the expression of MN proteins. The invention still further concerns antisense nucleic acid sequences that can be used to inhibit MN gene expression, and polymerase chain reaction (PCR) assays to detect genetic rearrangements.

28 Claims, 58 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 5972357

DOCUMENT-IDENTIFIER: US 5972357 A

TITLE: Healthy foods and cosmetics

DATE-ISSUED: October 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yamaguchi; Fumio	Noda	N/A	N/A	JP
Saito; Makoto	Noda	N/A	N/A	JP
Ishikawa; Hiroharu	Noda	N/A	N/A	JP
Kataoka; Shigehiro	Noda	N/A	N/A	JP
Ariga; Toshiaki	Noda	N/A	N/A	JP

APPL-NO: 08/ 975713

DATE FILED: November 21, 1997

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	8-353869	December 19, 1996
JP	9-199119	July 10, 1997
JP	9-199120	July 10, 1997

US-CL-CURRENT: 424/401; 514/675 ; 514/678 ; 514/690 ; 514/724 ; 514/729 ; 514/730

ABSTRACT:

The present invention relates to healthy foods and cosmetics. More particularly, it relates to healthy foods and cosmetics containing a polyisoprenylated benzophenone derivatives as effective ingredients and having a variety of functions for maintaining health such as anti-ulcer activity, the Maillard reaction inhibiting activity, anti-oxidation activity, reactive oxygen species scavenging activity, and anti-tumor promotion activity.

5 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Detailed Description Text - DETX:

The EBV potentially infected human lymphoblasts (Raji) were first prepared in a concentration of 5.times.10.sup.5 cell/ml, and cultured in an RPMI-1640 medium

to which 3 mM n-butyric acid (**inducer) and 50 nM TPA (12-O-tetradecanoylphorbol-13-acetate) (promoter**) were added in an atmosphere of 5% carbon dioxide and 95% air under at a temperature of 37.degree. C. for 48 hours. The cells in which EBV-EA had been induced were detected microscopically by indirect immunofluorescence with the serum of a nasopharyngeal carcinoma (NPC) patient. In this system, various concentrations (8 .mu.g/ml, 40 .mu.g/ml, and 200 .mu.g/ml) of the test substance (garcinol sample shown in Referential Example 1) dissolved in DMSO (dimethylsolfoxide) were added together with the promoter to the cells. The activity of suppressing the induction of the Epstein-Barr virus early antigen was defined as the decreasing rate of the cells in which EBV-EA had been induced.

US-PAT-NO: 5972353

DOCUMENT-IDENTIFIER: US 5972353 A

TITLE: MN proteins, polypeptides, fusion proteins and fusion polypeptides

DATE-ISSUED: October 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CZ
Pastorekova; Silvia	Bratislava	N/A	N/A	SK
Pastorek; Jaromir	Bratislava	N/A	N/A	SK

APPL-NO: 08/ 477504

DATE FILED: June 7, 1995

PARENT-CASE:

This is a continuation-in-part of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now pending U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CS	709-92	March 11, 1992

US-CL-CURRENT: 424/277.1; 424/138.1 ; 424/139.1 ; 514/12 ; 530/300 ; 530/350 ; 530/387.1 ; 530/388.8

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides. Also provided are nucleic acid probes for the MN gene as well as test kits comprising said probes. The invention also concerns vaccines comprising MN proteins/polypeptides which are effective to immunize a vertebrate against neoplastic diseases associated with the expression of MN proteins. The invention still further concerns antisense nucleic acid sequences that can be used to inhibit MN gene expression, and

polymerase chain reaction (PCR) assays to detect genetic rearrangements.

53 Claims, 41 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 5955369

DOCUMENT-IDENTIFIER: US 5955369 A

TITLE: Method for the determination of mutant restriction enzymes

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mallonee; Richard L.	Baltimore	MD	N/A	N/A

APPL-NO: 08/ 895074

DATE FILED: July 16, 1997

US-CL-CURRENT: 435/6; 435/18

ABSTRACT:

The present invention is directed to a method for the determination of mutant restriction enzymes which comprises incubating restriction enzymes under non-native conditions with a labeled double stranded oligonucleotide to a solid support to form an enzyme-oligonucleotide complex and detecting the label to determine cleavage of the oligonucleotide by mutant enzymes.

13 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX:

In this example, large numbers of bacterial colonies are screened for the production of mutant proteins/enzymes. A culture of bacteria carrying the mutated gene of interest is plated out as follows. A nitrocellulose membrane (NC) is prepared as in Example 1 by coating with the same BSA-biotin-streptavadin-biotin-oliognucleotide complex. The NC membrane is then placed on an agar plate containing LB medium (Luria-Bertani medium), antibiotic and isopropylthio-.beta.-D-galactoside (IPTG). A cellulose acetate filter is placed on top of the coated NC membrane. The bacteria, in this example, recombinant E. coli, (this strain harbors a vector containing the trc **promoter for expression of HincII and is inducible with IPTG), is spread on the cellulose acetate** filter at a dilution to form single colonies. These plates are then incubated at 37.degree. C. for at least 16 hours to allow bacterial

colonies to form and grow. The cellulose acetate membrane containing the colonies is removed and retained for positive colony isolation. The NC membrane is removed and developed, using antibodies at dilutions described in Example 1. Membranes are washed five times with PBS. They are then developed with 5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium (Sigma Fast BCIP/NBT made by Sigma Chemical Company) as a precipitable substrate. A "negative spot" (absence of color) created by a single colony on a background of precipitated color indicates the restriction enzyme being produced has cleaved the double stranded oligonucleotide.

US-PAT-NO: 5955075

DOCUMENT-IDENTIFIER: US 5955075 A

TITLE: Method of inhibiting tumor growth using antibodies to MN protein

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zavada; Jan	Prague	N/A	N/A	CS
Pastorekova; Silvia	Bratislava	N/A	N/A	SK
Pastorek; Jaromir	Bratislava	N/A	N/A	SK

APPL-NO: 08/ 481658

DATE FILED: June 7, 1995

PARENT-CASE:

This is a continuation-in-part of now pending U.S. Ser. No. 08/260,190 (filed Jun. 15, 1994), which, in turn, is a continuation-in-part of now pending U.S. Ser. No. 08/177,093 (filed Dec. 30, 1993), which is in turn a continuation-in-part of U.S. Ser. No. 07/964,589 (filed Oct. 21, 1992), which issued as U.S. Pat. No. 5,387,676 on Feb. 7, 1995, but from which a now pending continuation U.S. Ser. No. 08/335,469 was filed on Nov. 7, 1994.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CS	709-92	March 11, 1992

US-CL-CURRENT: 424/138.1; 424/133.1 ; 424/139.1 ; 424/141.1 ; 424/152.1 ; 530/387.1 ; 530/388.1 ; 530/388.2

ABSTRACT:

A new gene--MN--and proteins/polypeptides encoded therefrom are disclosed. Recombinant nucleic acid molecules for expressing MN proteins/polypeptides and recombinant proteins are provided. Expression of the MN gene is disclosed as being associated with tumorigenicity, and the invention concerns methods and compositions for detecting and/or quantitating MN antigen and/or MN-specific antibodies in vertebrate samples that are diagnostic/prognostic for neoplastic and pre-neoplastic disease. Test kits embodying the immunoassays of this invention are provided. MN-specific antibodies are disclosed that can be used diagnostically/prognostically, therapeutically, for imaging, and/or for affinity purification of MN proteins/polypeptides.

25 Claims, 58 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 31

---------- KWIC ---------

Detailed Description Text - DETX:

No detectable CAT activity was observed in additional experiments using increasing amounts of transfected plasmids (from 2 to 20 g DNA per dish) and prolonged periods of cell incubation after transcription. Increased cell density also did not improve the results (in contrast to the expectations based on density-dependent expression of native MN protein in HeLa cells). Since we found consensus sequences for transcription factors AP2 and AP1 in the putative MN **promoter, we studied the effect of their inducers dexamethasone (1 m) and phorbol ester phorbol 12-myristate 13-acetate** (PMA 50 ng/ml) on CAT activity. However, the MN promoter was unresponsive to those compounds.

US-PAT-NO: 5910629

DOCUMENT-IDENTIFIER: US 5910629 A

TITLE: Chimeric genes comprising a fungus-responsive element

DATE-ISSUED: June 8, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Strittmatter; Gunter	Cologne	N/A	N/A	DE

APPL-NO: 08/ 737298

DATE FILED: January 6, 1997

PCT-DATA:
APPL-NO: PCT/EP95/00868
DATE-FILED: March 9, 1995
PUB-NO: WO96/28561
PUB-DATE: Sep 19, 1996
371-DATE: Jan 6, 1997
102(E)-DATE: Jan 6, 1997

US-CL-CURRENT: 800/279; 435/418 ; 435/419 ; 435/468 ; 435/69.1 ; 536/23.6 ; 536/24.1 ; 536/24.5 ; 800/265 ; 800/268 ; 800/285 ; 800/287 ; 800/298

ABSTRACT:

The present invention provides improved fungus-responsive chimeric genes for the production of transgenic plants which have plant cells surrounding the site of fungal infection that become capable of killing, disabling or repelling the fungus or that are themselves killed or rendered unsuitable for the fungus to feed upon, thereby preventing the spread of the fungus infection.

27 Claims, 1 Drawing figures

Exemplary Claim Number: 1,8,11,20

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX:

Particularly preferred fungus-responsive prp1-1 elements of this invention are those termed delB34 (nucleotide positions 140 to 273 in SEQ ID No. 1), delB35 (nucleotide positions 100 to 273 in SEQ ID No. 1), and delB51 (nucleotide

positions 176 to 273 in SEQ ID No. 1), that are significantly less responsive to salicylic acid and indolyl **acetate application (2- to 3-fold lower induction) when compared to the 273 bp prp1-1 promoter,** even more preferred fungus-responsive prp1-1 elements of this invention are those termed delX4 (nucleotide positions 1 to 239 in SEQ ID No. 1) and delX5 (nucleotide positions 1 to 153 in SEQ ID No. 1), since these portions have substantially (i.e., drastically) lost the expression observed in root tips with the 273 bp prp1-1 promoter (WO 93/119188, e.g., no histochemically detectable GUS protein by a delX4- or delX5-GUS chimeric gene in roots), as well as being significantly less responsive to salicylic acid and indole **acetate application (a 30- to 40-fold lower induction) when compared to the 273 bp prp1-1 promoter,** while still retaining a significant fungal responsiveness. Also included in this definition are natural or artificial promoter elements with a DNA sequence that is substantially similar to any of the delX4, delX5, delB34, delB35, and delB51 DNA sequences defined above, i.e., having some nucleotides deleted, replaced or added provided substantially the same promoter characteristics are retained.

US-PAT-NO: 5874464

DOCUMENT-IDENTIFIER: US 5874464 A

TITLE: Conformationally constrained diacylglycerol analogues

DATE-ISSUED: February 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Marquez; Victor E.	Gaithersburg	MD	N/A	N/A
Lee; Jeewoo	Rockville	MD	N/A	N/A
Sharma; Rajiv	Rockville	MD	N/A	N/A
Wang; Shaomeng	Rockville	MD	N/A	N/A
Milne; George W. A.	Bethesda	MD	N/A	N/A
Nicklaus; Marc C.	Elkridge	MD	N/A	N/A
Blumberg; Peter M.	Frederick	MD	N/A	N/A
Lewin; Nancy E.	Rockville	MD	N/A	N/A

APPL-NO: 08/ 372602

DATE FILED: January 13, 1995

US-CL-CURRENT: 514/473; 514/372 ; 514/424 ; 514/439 ; 514/471 ; 548/214 ; 548/550 ; 548/551 ; 549/321 ; 549/323 ; 549/40

ABSTRACT:

Conformationally constrained diacylglycerol analogues, pharmaceutical compositions comprising such analogues, and methods of using such analogues as agonists and antagonists of protein kinase C.

12 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX:

Tumor **promoters, such as phorbol esters, e.g., 12-O-tetradecanoylphorbol-13-acetate (TPA), and aplysiatoxins, have been shown to activate** PK-C by acting as stable, highly potent DAG equivalents. Unlike DAGS, whose presence in the cell membrane is transient, phorbol esters are not metabolized and are, therefore, able to activate PK-C chronically, bypassing the DAG pathway. Chronic constitutive activation of PK-C is associated with resistance of cancerous cells to antitumor drugs.

US-PAT-NO: 5851764

DOCUMENT-IDENTIFIER: US 5851764 A

TITLE: Human prostate tumor inducing gene-1 and uses thereof

DATE-ISSUED: December 22, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fisher; Paul B.	Scarsdale	NY	N/A	N/A
Shen; Ruoqian	New York	NY	N/A	N/A

APPL-NO: 08/ 371377

DATE FILED: January 11, 1995

PARENT-CASE:

This application is a continuation-in-part of U.S application Ser. No. 08/351,888, filed Dec. 8, 1994, which is a continuation of U.S. Ser. No. 08/225,493, filed Apr. 11, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/106,323, filed Aug. 13, 1993, now abandoned, which is a continuation of U.S. Ser. No. 07/603,804, filed Oct. 25, 1990, now abandoned, the contents of which are hereby incorporated by reference.

US-CL-CURRENT: 435/6; 435/91.1 ; 436/94 ; 536/23.5 ; 536/24.1 ; 536/24.31 ; 536/24.33 ; 536/25.3

ABSTRACT:

This invention provides a method for preparing a hybridoma cell line which produces an antibody capable of specifically binding to a cell surface-expressed protein which expresses on the surface of one cell type but not the other. This invention also provides a method for preparing a hybridoma cell line which produces an antibody capable of specifically binding to a cell surface-expressed protein. This invention provides a method to prepare a hybridoma cell line which specifically recognizes and binds to a tumor associated antigen associated with a neoplastic, human cell. This invention also provides a method of preparing DNA encoding a cell surface antigen associated with a neoplastic, human cell. This invention further provides an isolated mammalian nucleic acid molecule having the sequence of Prostate Carcinoma Tumor Antigen Gene-1. This invention also provides an isolated mammalian nucleic acid molecules having the sequence of Prostate Tumor Inducing Gene-1. This invention provides an isolated mammalian nucleic acid molecules having the sequence of Prostate Tumor Inducing Gene-2. Finally, this invention provides an isolated mammalian nucleic acid molecules having the sequence of Prostate Tumor Inducing Gene-1.

8 Claims, 27 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 23

---------- KWIC ---------

Detailed Description Text - DETX:

PTI-1: Using primer sequences for bases present in the unique 630 bp 5' region of PTI-1 (A and L) and primer sequences corresponding to the elongation factor-1 alpha region of PTI-1 and RT-PCR approaches, the following additional information is currently available relative to PTI-1: (A) Tissue distribution studies (using tissue poly A.sup.+ mRNA blots from Clontech) have been performed using the A and L primers and a region corresponding to the elongation factor-1 alpha homologous region of PTI-1 as probes. The unique region of PTI-1 is only expressed in skeletal muscle and colon tissue, whereas the elongation factor-1 alpha hybridizes with an mRNA present in all of the tissue samples. These include, spleen, thymus, prostate, testis, ovary, small intestine, colon, peripheral blood leukocyte, heart, brain, placenta, lung, liver, skeletal muscle, kidney and pancreas. These studies reinforce our previous observations that the unique region of PTI-1 is not expressed in normal human prostate. (B) Expression of PTI-1 (A and L primers) is reduced in LNCaP cells treated with: a phorbol ester tumor **promoter (12-0-tetradecanoyl-phorbol -13-acetate (TPA), that induces** apoptosis in LNCaP cells; suramin; epidermal growth factor; transforming growth factor-alpha; or the synthetic androgen R1881. Using primers for prostate specific antigen (PSA) reductions in PTI-1 mRNA levels using the same agents are also apparent in LNCaP cells. These results suggest that similar changes inducing downregulation of PSA expression can also decrease PTI-1 expression in human prostate carcinoma cells. (C) Expression is apparent in human promyelocytic leukemia (HL-60) and an additional leukemic cell line K562. When induced to differentiate by TPA, PTI-1 expression decreases and is no longer apparent by 3 hr posttreatment in HL-60 cells. This change in mRNA levels after TPA treatment suggests that decreased expression of PTI-1 may be modulated as a function of growth arrest and terminal differentiation in HL-60 cells; (D) Expression is apparent in CREF cells transformed by diverse acting oncogenes, including wild-type 5 adenovirus (Ad5), mutant type 5 adenovirus (H5hr1), Ha-ras oncogene, v-src, human papilloma virus type 18 (HPV-18) and HPV-51. Using a dexamethasone (DEX) inducible Ad5 E1A transforming gene under the transcriptional control of a mouse mammary tumor virus promoter, expression of PTI-1 is only seen in the presence of DEX. Under these culturing conditions, DEX also results in EIA expression and transformation. These data indicate that induction of PTI-1 directly correlates with transformation induced by mechanistically different oncogenes. Figure of Northern blot; FIG. 11).

US-PAT-NO: 5837728

DOCUMENT-IDENTIFIER: US 5837728 A

TITLE: 9-cis retinoic acid esters and amides and uses thereof

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Purcell; William P.	Memphis	TN	N/A	N/A

APPL-NO: 08/ 380011

DATE FILED: January 27, 1995

US-CL-CURRENT: 514/529; 514/559 ; 554/221

ABSTRACT:

Esters and amides of 9-cis-retinoic acid are synthesized, formulated into pharmaceutically acceptable carriers and administered for the treatment of acne vulgaris, cystic acne, hyper-pigmentation, hypo-pigmentation, psoriasis, dermal and epidermal hypoplasia and kerotoses, the reduction of wrinkling of the skin as an incident of aging and actinic damage, normalization of the production of sebum, the reduction of enlarged pores, promoting the rate of wound healing, limiting of scar tissue formation during healing and the like. They are additionally useful for treatment or amelioration of the same additional classes of skin disorders as is retinoic acid itself and other retinoids. These disorders include ichthyoses (e.g., ichthyosis hystrix, epidermolytic hyperkeratosis, and lamellar ichthyosis), follicular disorders (e.g., pseudofolliculites, senile comedones, nevus comidonicas, and trichostatis spinulosa), benign epithelial tumors (e.g., flat warts, trichoepithelioma, and molluscum contagiosum), perforated dematoses (e.g., elastosis perforans seripiginosa and Kyrles disease), and disorders of keratinization (e.g., Dariers disease, keratoderma, hyperkeratosis plantaris, pityriasis rubra pilaris, lichen planus acanthosis nigricans, and psoriasis). The esters and amides of 9-cis-retinoic acid are also effective for the non-irritating treatment of effects attributable to aging and particularly to photodamage and photoaging. The use of these compounds extends to non-irritating treatments involving the retardation and reversal of additional dermal and cosmetic conditions which are ameliorated by tretinoin such as the effacement of wrinkles, improvement in appearance, namely color and condition of the skin, spots caused from exposure to the sun as well as other skin disorders. The esters and amides of 9-cis-retinoic acid are exceptionally active when compared to other retinoids employed for such indications, and are also exceptionally safe in effective therapeutic doses in contrast to other retinoids.

40 Claims, 0 Drawing figures

Exemplary Claim Number: 1,12

---------- KWIC ---------

Detailed Description Text - DETX:

The ODC/Retinoid Bioassay is based on the method of Verma, A. K. and Boutwell, R. K., Cancer Res. (1977) 37:2196-2201. The ODC assay measures a compounds effect on the prevention of the induction of ODC, namely the effect of the retinoid compound on the inhibition of the tumor **promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) induced** ODC activity. The assay is carried out using CD-1 mice (aged 7 to 9 weeks). The dorsal hair of the mice is shaved 3-4 days before testing. Four mice are used for each point. The test retinoids, at one of two dose levels (1.7 and 17 nmoles) dissolved in 0.2 ml of acetone is applied topically to the back of each shaved mouse. A single dose of TPA (17 nM) is applied to the back of each treated mouse 30 minutes later. Control groups are treated with either acetone alone, TPA, or tretinoin. The mice are sacrificed by cervical dislocation 5 hours after TPA treatment.

US-PAT-NO: 5830692

DOCUMENT-IDENTIFIER: US 5830692 A

TITLE: Expression system which can be regulated

DATE-ISSUED: November 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bock; August	Geltendorf	N/A	N/A	DE
Mayer; Dagmar	Munchen	N/A	N/A	DE
Schlensog; Verena	Ismaning	N/A	N/A	DE
Candussio; Anton	Munchen	N/A	N/A	DE

APPL-NO: 08/ 614686

DATE FILED: March 12, 1996

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
DE	195 10 930.9	March 24, 1995
DE	195 14 056.7	April 13, 1995

US-CL-CURRENT: 435/69.1; 435/252.3 ; 435/252.33 ; 435/320.1 ; 536/23.1 ; 536/24.1

ABSTRACT:

An expression system can be **regulated by acetate, pH and oxygen, which expression system includes a trans-acting regulator protein and a promoter** which can be activated by this protein. Any desired structural genes are maximally expressed under the control of the expression system at an oxygen partial pressure, pO.sub.2, of 0-5% and a pH of 6.0-6.5, and in the presence of acetate at a concentration of 40-60 mM. There is also a process for preparing this expression system, and a process for using this expression system.

12 Claims, 10 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 10

---------- KWIC ---------

Abstract Text - ABTX:

An expression system can be **regulated by acetate, pH and oxygen, which**

expression system includes a trans-acting regulator protein and a promoter which can be activated by this protein. Any desired structural genes are maximally expressed under the control of the expression system at an oxygen partial pressure, pO.sub.2, of 0-5% and a pH of 6.0-6.5, and in the presence of acetate at a concentration of 40-60 mM. There is also a process for preparing this expression system, and a process for using this expression system.

Brief Summary Text - BSTX:

The present invention relates to an expression system which can be **regulated by acetate, pH and oxygen, which expression system comprises a trans-acting regulator protein and a promoter** which can be activated by this protein, wherein the regulator protein encompasses an amino acid sequence which is at least 75% homologous with the amino acid sequence SEQ ID NO:1, and the promoter encompasses a DNA sequence which is at least 95% homologous with the bases 315 to 397 of the DNA sequence SEQ ID NO:2.

Brief Summary Text - BSTX:

The present invention furthermore relates to a regulator protein which brings about optimal **activation of the bud promoter from Klebsiella terrigena (DSM2687) in association with oxygen limitation and in the presence of acetate** and at a pH of the culture medium of from pH 6.0 to pH 6.5.

Detailed Description Text - DETX:

In order to identify plasmids encoding a transacting factor which **activates the bud promoter in the presence of acetate,** E. coli BL142 was transformed with the Klebsiella terrigena gene library by means of electroporation (Fiedler and Wirth (1988) Analytical Biochemistry 170, pp. 38-44). The transformation mixtures were spread on so-called indicator plates (potassium phosphate-buffered TGYEP agar (pH 6.5) containing 0.4% glucose, 40 mM acetate, 1 mM X-Gal and ampicillin (100 .mu.g/ml)) and were incubated at 37.degree. C. Due to its very weak .beta.-galactosidase activity (Table 5), E. coli BL142 forms pale-blue colonies on these indicator plates. By contrast, after transformation, one clone formed a deep dark blue colony. It contained the plasmid pBAK1 (FIG. 4), which carries an approximately 1.8 kb-sized Sau3A fragment from Klebsiella terrigena. For the subsequent analyses, a 1.8 kb-sized HindIII fragment, which contains a 350 bp-sized fragment of vector pBR322 and a 1.45 kb-sized fragment from Klebsiella terrigena, was isolated from pBAK1 (See FIG. 4); the protruding ends of the fragment were filled in with Klenow polymerase. The fragment was then ligated, in both orientations, into plasmid pUC19 which had been linearized with SmaI. The resulting plasmids, which also impart a blue coloration to E. coli BL142 colonies on indicator plates, were designated pBAK14 and pBAK16 (FIGS. 5 and 6).

US-PAT-NO: 5808001

DOCUMENT-IDENTIFIER: US 5808001 A

TITLE: Human ice homolog antibodies and compositions thereof

DATE-ISSUED: September 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Braxton; Scott Michael	San Mateo	CA	N/A	N/A
Delegeane; Angelo M.	Hayward	CA	N/A	N/A
Diep; Dinh	San Francisco	CA	N/A	N/A

APPL-NO: 08/ 900491

DATE FILED: July 25, 1997

PARENT-CASE:

This application is a divisional application of application No. 08/443,865 filed May 31, 1995, now U.S. Pat. No. 5,654,146.

US-CL-CURRENT: 530/387.1; 530/388.1

ABSTRACT:

The present invention provides nucleotide and amino acid sequences that identify and encode a new human interleukin-1 converting enzyme homolog (ICEY). The present invention also provides for antisense molecules to the nucleotide sequences which encode ICEY, expression vectors for the production of purified ICEY, antibodies capable of binding specifically to ICEY, hybridization probes or oligonucleotides for the detection of ICEY-encoding nucleotide sequences, genetically engineered host cells for the expression of ICEY, diagnostic tests for activation of monocyte/macrophages based on ICEY-encoding nucleic acid molecules, and use of the protein to produce antibodies capable of binding specifically to the protein and use of the protein to screen for inhibitors.

2 Claims, 7 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 7

--------- KWIC ---------

Brief Summary Text - BSTX:

Many human myeloid and myelomonocytic cell lines retain some ability to differentiate into more mature phenotypes in response to various internal stimuli including growth factors, lymphokines, cytokines, vitamin D derivatives, and tumor promoters and external agents such as trauma, smoking, UV irradiation, asbestos exposure, and steroids. THP-1 cells treated with the tumor **promoter 12-O-tetradecanoyl-phorbol-13 acetate (TPA) are induced** to stop proliferating and differentiate into macrophage-like cells which mimic native monocyte-derived macrophages both morphologically and physiologically.

US-PAT-NO: 5786362

DOCUMENT-IDENTIFIER: US 5786362 A

TITLE: Method of treating Hormone independent cancer

DATE-ISSUED: July 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Krongrad; Arnon	Surfside	FL	N/A	N/A

APPL-NO: 08/ 260884

DATE FILED: June 16, 1994

US-CL-CURRENT: 514/280

ABSTRACT:

Activation of the c-fos promoter and the serum response element (SRE) in androgen independent cancer cells has been demonstrated. In androgen dependent cells, direct activation of protein kinase C (PKC) or serum response factor (SRF) activated the c-fos promoter or SRE and caused androgen independent expression of an androgen target promoter. The highly specific PKC inhibitor chelerythrine selectively killed androgen independent cells. Expression of mutant SRF cDNA's inhibited activation of the SRE in prostate cancer cells. These reagents demonstrate the feasibility of both chemotherapy and gene therapy in interfering with intracellular pathways on which androgen independent cells are dependent; i.e. a strategy is outlined for treating hormone independent cancer in which the PKC-SRE pathway is disrupted by either chemotherapy or gene therapy.

2 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

---------- KWIC ---------

Detailed Description Text - DETX:

In the androgen independent cells, basal activity of the full-length c-fos promoter was elevated in comparison to that seen in LNCap cells (FIG. 1a). Basal levels were 47-, 35-, 4-, 8-, and 17-fold higher in TAC, PPC-1, DU145, ALVA-31, and MFM-M, respectively (FIG. 1a). This was associated with reduced sensitivity to phorbol ester. In the androgen dependent LNCap cells, c-fos

promoter was inducible 256-fold by the phorbol ester phorbol 12-myristate 13 acetate ("PMA") (FIG. 1a). By contrast, in the androgen independent cells TAC, PPC-1, DU145, ALVA-31, and MFM-M the induction with PMA was 1.8-, 1.8-, 2.9-, 1.7-, and 1.6-fold, respectively. Elevated basal expression associated with noninducibility by phorbol ester is defined to indicate activation.

US-PAT-NO: 5654146

DOCUMENT-IDENTIFIER: US 5654146 A

TITLE: Human ice homolog

DATE-ISSUED: August 5, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Braxton; Scott Michael	San Mateo	CA	N/A	N/A
Delegeane; Angelo M.	Hayward	CA	N/A	N/A
Diep; Dinh	San Francisco	CA	N/A	N/A

APPL-NO: 08/ 443865

DATE FILED: May 31, 1995

US-CL-CURRENT: 435/6; 435/183 ; 435/320.1 ; 435/358 ; 435/69.2 ; 435/7.4 ; 536/23.2

ABSTRACT:

The present invention provides nucleotide and amino acid sequences that identify and encode a new human interleukin-1 converting enzyme homolog (ICEY). The present invention also provides for expression vectors for the production of purified ICEY, hybridization probes for the detection of ICEY-encoding nucleotide sequences, genetically engineered host cells for the expression of ICEY, diagnostic tests for ICEY or for polynucleotides encoding ICEY, and use of the protein to produce antibodies capable of binding specifically to the protein and use of the protein to screen for inhibitors.

10 Claims, 6 Drawing figures

Exemplary Claim Number: 8

Number of Drawing Sheets: 7

---------- KWIC ---------

Brief Summary Text - BSTX:

Many human myeloid and myelomonocytic cell lines retain some ability to differentiate into more mature phenotypes in response to various internal stimuli including growth factors, lymphokines, cytokines, vitamin D derivatives, and tumor promoters and external agents such as trauma, smoking, UV irradiation, asbestos exposure, and steroids. THP-1 cells treated with the tumor **promoter 12-O-tetradecanoyl-phorbol-13 acetate (TPA) are induced** to stop

proliferating and differentiate into macrophage-like cells which mimic native monocyte-derived macrophages both morphologically and physiologically.

US-PAT-NO: 5637462

DOCUMENT-IDENTIFIER: US 5637462 A

TITLE: Cathepsin C homolog

DATE-ISSUED: June 10, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Coleman; Roger	Mountain View	CA	N/A	N/A
Braxton; Scott M.	San Mateo	CA	N/A	N/A
Seilhamer; Jeffrey J.	Los Altos Hills	CA	N/A	N/A

APPL-NO: 08/ 426428

DATE FILED: April 19, 1995

US-CL-CURRENT: 435/6; 435/91.2 ; 536/22.1 ; 536/23.1 ; 536/24.3 ; 536/24.31

ABSTRACT:

The present invention provides nucleotide and amino acid sequences that identify and encode a new cathepsin C homolog (RCP) expressed in THP-1 cells. The present invention also provides for antisense molecules to the nucleotide sequences which encode RCP, expression vectors for the production of purified RCP, antibodies capable of binding specifically to RCP, hybridization probes or oligonucleotides for the detection of RCP-encoding nucleotide sequences, genetically engineered host cells for the expression of RCP, diagnostic tests for activation of monocyte/macrophages based on RCP-encoding nucleic acid molecules, and use of the protein to produce antibodies capable of binding specifically to the protein and use of the protein to screen for inhibitors.

5 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX:

Many human myeloid and myelomonocytic cell lines retain some ability to differentiate into more mature phenotypes in response to various internal stimuli including growth factors, lymphokines, cytokines, vitamin D derivatives, and tumor promoters and external agents such as trauma, smoking, UV irradiation, asbestos exposure, and steroids. THP-1 cells treated with the

tumor **promoter 12-O-tetradecanoyl-phorbol-13 acetate (TPA) are induced** to stop proliferating and differentiate into macrophage-like cells which mimic native monocyte-derived macrophages both morphologically and physiologically.

US-PAT-NO: 5591773

DOCUMENT-IDENTIFIER: US 5591773 A

TITLE: Inhibition of cataract formation, diseases resulting from oxidative stress, and HIV replication by caffeic acid esters

DATE-ISSUED: January 7, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Grunberger; Dezider	Teaneck	NJ	N/A	N/A
Frenkel; Krystyna	Woodmere	NY	N/A	N/A

APPL-NO: 08/ 212569

DATE FILED: March 14, 1994

US-CL-CURRENT: 514/532; 514/912

ABSTRACT:

A method of inhibiting the formation of a cataract in an eye by contacting the eye with a compound having the structure: ##STR1## is described. Also described is a method of inhibiting the progression of cataract formation in an eye. Methods comprising administering a pharmaceutical composition comprising the above compound to inhibit the formation of a cataract in the eye of a subject and to inhibit progression of cataract formation in the eye of a subject are also described. The above compound also prevents diseases resulting from oxidative stress, including diseases comprising tumor formation resulting from oxidative stress, and also inhibits the progression of diseases resulting from oxidative stress. The above compound may furthermore be used to treat an HIV infection when combined in a pharmaceutical composition with a substance which inhibits HIV replication.

30 Claims, 13 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 13

---------- KWIC ---------

Brief Summary Text - BSTX:

It has recently been shown that the phorbol ester-type tumor **promoters (12-O-tetradecanoylphorbol-13-acetate, hereinafter TPA) induce** H.sub.2 O.sub.2 production in mouse skin as well as cause oxidation of DNA bases in vivo

(20-22). In addition, it has been found that agents possessing anti-tumor-promoting properties in vivo, also suppress inflammatory processes. Processes suppressed by such agents include infiltration of polymorphonuclear leukocytes (hereinafter PMNs), reactive oxygen species production, and oxidation of DNA bases (20-22), as well as induction of ornithine decarboxylase (ODC) and edema (23-26). A number of known anti-tumor promoters that possess all or some of those properties have been isolated from biological sources, and include sarcophytol A (isolate from marine soft coral) (27, 28), (-)-epigallocatechin gallate (EGCG, a polyphenol from green tea) (26, 29, 30), curcumin (a spice) (24, 25), and caffeic acid (24, 25).

US-PAT-NO: 5374616

DOCUMENT-IDENTIFIER: US 5374616 A

TITLE: Compositions containing sphingosylphosphorylcholine and the use thereof as a cellular growth factor

DATE-ISSUED: December 20, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Spiegel; Sarah	Potomac	MD	N/A	N/A
Desai; Naishadh N.	Washington	DC	N/A	N/A

APPL-NO: 07/ 778662

DATE FILED: October 18, 1991

US-CL-CURRENT: 514/4; 435/405 ; 514/114 ; 514/12

ABSTRACT:

A pharmaceutical composition for promoting cellular proliferation in a mammal, which comprises:

a) an amount of an active ingredient effective to promote said cellular proliferation, and

b) a pharmaceutically acceptable carrier, said active ingredient comprising, at least, sphingosylphosphorylcholine.

3 Claims, 7 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 3

---------- KWIC ---------

Detailed Description Text - DETX:

In accordance with the present invention, it has been surprisingly discovered that sphingosylphosphorylcholine and pharmaceutical compositions containing the same exhibit a remarkably potent mitogenic effect for a wide variety of cell lines. Quite surprisingly, it has been discovered that sphingosylphosphorylcholine is a much more potent cellular growth factor than other known growth factors, including sphingosine and sphingosine-1-phosphate, and also acts synergistically with other agents such as insulin, epidermal

growth factor (EGF), fibroblast growth factor (FGF) and the tumor **promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), to induce** cellular proliferation in mammalian cells.

US-PAT-NO: 5347046

DOCUMENT-IDENTIFIER: US 5347046 A

TITLE: Catalyst and process for using same for the preparation of unsaturated carboxylic acid esters

DATE-ISSUED: September 13, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
White; James F.	Hudson	OH	N/A	N/A
Slawski; Barbara	Parma	OH	N/A	N/A
White; Geoffrey	Shaker Heights	OH	N/A	N/A

APPL-NO: 08/ 067445

DATE FILED: May 25, 1993

US-CL-CURRENT: 560/245

ABSTRACT:

Disclosed are catalyst compositions comprising (i) one or more palladium group metals and/or compounds thereof; (ii) gold and/or compounds thereof; and (iii) optionally, an effective amount of one or more promoters selected from the group consisting of copper, nickel, cobalt, iron, manganese, lead, silver and compounds thereof. Preferably these catalyst compositions contain one or more promoters wherein the gram ratio of metal in the promoter to palladium group metal is up to about 0.4, wherein the catalysts are deposited on a support material and said support material is treated with one or more alkali metal bases and one or more alkali metal silicates prior to said deposition.

Also described are processes for preparing ethylenically unsaturated esters comprising reacting in the vapor phase at least one olefinic compound with at least one carboxylic organic acid and molecular oxygen in the presence of an effective amount of the foregoing catalyst compositions.

17 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX:

The catalysts of this invention may also contain one or more alkali or alkaline earth salts of an organic acid such as lithium, sodium, calcium or potassium

acetate as a promoter and activator. These organic acid salts may be added to the catalyst in amounts up to 50 grams per liter of catalyst and preferably in the range of 15 to 35 grams per liter of catalyst.

US-PAT-NO: 5179056

DOCUMENT-IDENTIFIER: US 5179056 A

TITLE: Production of alkenyl alkanoate catalysts

DATE-ISSUED: January 12, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bartley; William J.	Charleston	WV	N/A	N/A

APPL-NO: 07/ 793131

DATE FILED: November 18, 1991

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION This application is a continuation-in-part of U.S. patent application Ser. No. 696,215; filed May 6, 1991.

US-CL-CURRENT: 502/170; 502/330 ; 560/241.1 ; 560/245

ABSTRACT:

This invention provides a process for producing improved catalysts for the production of alkenyl alkanoates by the reaction of an alkene, an alkanoic acid and an oxygen-containing gas. The catalysts contain palladium, gold and a potassium promoter and are characterized by a reduced sodium content which results in increased catalyst activity. The reduced sodium content is obtained by using essentially sodium-free starting materials in the process for producing the catalysts.

6 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX:

In the practice of the process of the present invention, sodium-containing, water-soluble palladium and/or gold compounds can usually be employed since they are usually not used in amounts that result in catalysts having substantial amounts of sodium. The principal sources of sodium in alkenyl

alkanoate catalysts are sodium-containing precipitating agents (e.g., sodium metasilicate) and/or sodium-containing **promoters or activators (e.g., sodium acetate**). To a lesser extent, some supports and some reducing agents (e.g., sodium borohydride) can introduce substantial amounts of sodium into the catalyst. Accordingly, in the practice of this invention, essentially sodium-free precipitating agents (e.g., potassium hydroxide), promoters (e.g., potassium acetate), reducing agents (e.g., hydrazine) and carriers are employed. When using potassium hydroxide as the precipitating agent, a suitable potassium salt (e.g., potassium acetate) can also be used in the precipitating step to aid in displacement by potassium of any sodium bound on the carrier. Preferably the potassium hydroxide and the potassium salt are employed in an aqueous solution. The salt is used in an amount that provides from 1 to 10 weight percent potassium based on the total weight of the solution. Care should be exercised to ensure that the resulting catalyst does not contain so much potassium that catalyst activity is less than desired.

US-PAT-NO: RE34075

DOCUMENT-IDENTIFIER: US RE34075 E

TITLE: Dermal uses of trans-retinoids for the treatment of cancer

DATE-ISSUED: September 22, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Purcell; William P.	Memphis	TN	N/A	N/A
Parish; Harlie A.	Memphis	TN	N/A	N/A

APPL-NO: 07/ 732091

DATE FILED: July 18, 1991

REISSUE-DATA:
US-PAT-NO: 04994491
DATE-ISSUED: February 19, 1991
APPL-NO: 284185
DATE-FILED: December 14, 1988

PARENT-CASE:

.ladd.CROSS-REFERENCE TO RELATED APPLICATION This application is a Continuation-in-Part of application Ser. No. 67,536, filed Jun. 29, 1987 (now U.S. Pat. No. 4,885,311, issued Dec. 5, 1989). .laddend.

US-CL-CURRENT: 514/529; 514/354 ; 514/355 ; 514/423 ; 514/425 ; 514/448 ; 514/461 ; 514/512 ; 514/522 ; 514/547 ; 514/548 ; 514/549

ABSTRACT:

The dermal use of non-irritating retinoids such as the esters and amides of 13-cis and 13-trans-retinoic acid for effecting the reduction and reversal of photoaging and skin cancer is disclosed.

5 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Detailed Description Text - DETX:

The ODC/Retinoid Bioassay is based on the method of Verma, A. K. and Boutwell, R. K., Cancer Res. (1977) 37:2196-2201. The ODC assay measures a compound's

effect on the prevention of the induction of ODC, namely the effect of the retinoid compound on the inhibition of the tumor **promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) induced** ODC activity. The assay was carried out using CD-1 mice (aged 7 to 9 weeks). The dorsal hair of the mice was shaved 3-4 days before testing. Four mice were used for each point. The test retinoids, at one of two dose levels (1.7 and 17 nmoles) dissolved in 0.2 ml of acetone was applied topically to the back of each shaved mouse. A single dose of TPA (17 nM) was applied to the back of each treated mouse 30 minutes later. Control groups were treated with either acetone alone, TPA, or tretinoin. The mice were killed by cervical dislocation 5 hours after TPA treatment.

US-PAT-NO: 5124356

DOCUMENT-IDENTIFIER: US 5124356 A

TITLE: Dermal uses of trans-retinoids for the treatment of photoaging

DATE-ISSUED: June 23, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Purcell; William P.	Memphis	TN	N/A	N/A
Parish, Jr.; Harlie A.	Memphis	TN	N/A	N/A

APPL-NO: 07/ 609742

DATE FILED: November 6, 1990

PARENT-CASE:

CROSS REFERENCE TO A RELATED APPLICATION This is a divisional of co-pending application Ser. No. 284,185, filed on Dec. 14, 1988, now U.S. Pat. No. 4,994,491, which is in turn a Continuation-in-Part of Applicants' co-pending application, Ser. No. 067,536, filed Jun. 29, 1987, now U.S. Pat. No. 4,885,311.

US-CL-CURRENT: 514/529; 514/354 ; 514/355 ; 514/423 ; 514/425 ; 514/448 ; 514/461 ; 514/512 ; 514/522 ; 514/547 ; 514/548 ; 514/549 ; 514/725

ABSTRACT:

The dermal use of non-irritating retinoids such as the esters and amides of 13-cis and 13-trans-retinoic acid for effecting the reduction and reversal of photoaging and skin cancer is disclosed.

5 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Detailed Description Text - DETX:

The ODC/Retinoid Bioassay is based on the method of Verma, A. K. and Boutwell, R. K., Cancer Res. (1977) 37:2196-2201. The ODC assay measures a compound's effect on the prevention of the induction of ODC, namely the effect of the retinoid compound on the inhibition of the tumor **promoter 12-0-tetradecanoylphorbol-13-acetate (TPA) induced** ODC activity. The assay was carried out using CD-1 mice (aged 7 to 9 weeks). The dorsal hair of the mice

was shaved 3-4 days before testing. Four mice were used for each point. The test retinoids, at one of two dose levels (1.7 and 17 nmoles) dissolved in 0.2 ml of acetone was applied topically to the back of each shaved mouse. A single dose of TPA (17 nM) was applied to the back of each treated mouse 30 minutes later. Control groups were treated with either acetone alone, TPA, or tretinoin. The mice were killed by cervical dislocation 5 hours after TPA treatment.

US-PAT-NO: 5124083

DOCUMENT-IDENTIFIER: US 5124083 A

TITLE: 3-substituted and 3,3-disubstituted 4-oxoretinoic acids and their esters

DATE-ISSUED: June 23, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shealy; Y. Fulmer	Birmingham	AL	N/A	N/A

APPL-NO: 07/ 575082

DATE FILED: August 30, 1990

US-CL-CURRENT: 514/529; 514/545 ; 514/547 ; 514/549 ; 514/725 ; 554/116 ; 554/118 ; 560/126 ; 560/51 ; 560/54 ; 568/824

ABSTRACT:

There are disclosed 3-substituted and 3,3-disubstituted all-trans-4-oxoretinoic acids and 3-substituted and 3,3-disubstituted 13-cis-4-oxoretinoic acids and their lower alkyl esters.

24 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Brief Summary Text - BSTX:

A bioassay in vivo for activity in the prevention of carcinogen-induced cancer is based on the reduction by a retinoid of the amount of ornithine decarboxylase (ODC) **induced in mouse skin by the tumor promoter 12-O-tetradecanoylphorbol 13-acetate** (TPA). Verma et al. (Cancer Research, Vol. 38, pages 793-801, 1978), reported that "application of the potent tumor-promoting agent 12-O-tetradecanoylphorbol 13-acetate (TPA) to mouse skin leads to a rapid and transient induction of epidermal ornithine decarboxylase activity". They state, further, that "inhibition of this enzyme activity by retinoids may be a simple and rapid in vivo test for assessing the potential prophylactic activity of new synthetic retinoids". The results of the ODC assay of 4-oxoretinoids of this invention are summarized in Table III (Example 26). All of the tested 4-oxoretinoid analogues reduced TPA-induced ODC activity. The compounds of Examples 2-4, 8, 11, 17, 18, and 20-23 reduced ODC activity to 22-47% of the ODC activity in the control mice and are, therefore,

very active in this assay for cancer chemopreventive activity.

US-PAT-NO: 5115096

DOCUMENT-IDENTIFIER: US 5115096 A

TITLE: Amphiregulin: a bifunctional growth modulating glycoprotein

DATE-ISSUED: May 19, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shoyab; Mohammed	Seattle	WA	N/A	N/A
McDonald; Vicki L.	Kent	WA	N/A	N/A
Bradley; James G.	Woodinville	WA	N/A	N/A
Plowman; Gregory D.	Seattle	WA	N/A	N/A

APPL-NO: 07/ 297816

DATE FILED: January 17, 1989

PARENT-CASE:

The present application is a continuation-in-part of copending application Ser. No. 181,884 filed Apr. 15, 1988 which is a continuation-in-part of copending application Ser. No. 148,327 filed Jan. 25, 1988 both now abandoned each of which is incorporated by reference herein in its entirety.

US-CL-CURRENT: 530/322; 530/324

ABSTRACT:

A novel cell growth regulatory factor, named Amphiregulin, is described. This extremely hydrophilic glycoprotein, having a median molecular weight of 22,500 daltons, demonstrates unusual biological activity. Amphiregulin is a bifunctional cell growth regulatory factor which exhibits potent inhibitory activity on DNA synthesis in neoplastic cells, yet promotes the growth of certain normal cells. The invention is based, in part, on the discovery that MCF-7 cells, when treated with the tumor promoting agent, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), express and secrete two distinct yet functionally equivalent forms of Amphiregulin. These two forms are structurally identical and perfectly homologous except that the truncated form lacks an amino-terminal hexapeptide found in the larger form. The Amphiregulin gene has been cloned and used to construct plasmids which direct the expression of bioactive Amphiregulin in transformed Escherichia coli cells. A wide variety of uses for Amphiregulin are encompassed by the present invention, including the treatment of wounds and cancers.

23 Claims, 21 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 35

---------- KWIC ---------

Brief Summary Text - BSTX:

Biologically active phorbol esters such as 12-0-tetradecanoyl-phorbol-13**-acetate (TPA) are potent tumor-promoters in vivo and elicit and modulate** a wide variety of biological and biochemical responses in vivo as well as in vitro (Blumberg, 1981, Crit. Rev. Toxicol. 9: 153-197; Slaga, 1983, Cancer Surv. 2: 595-612). It has been known for some time that TPA inhibits the growth of the human breast adenocarcinoma cell line MCF-7. In addition, TPA also alters the morphology of MCF-7 cells inasmuch as TPA treated cells exhibit the morphological characteristics of secretory cells (Osborne, et al., 1981, J. Clin. Invest. 67: 943-951; Valette et al., 1987, Cancer Res. 47: 1615-1620).

US-PAT-NO: 5049584

DOCUMENT-IDENTIFIER: US 5049584 A

TITLE: Dermal uses of cis-retinoids for the treatment of cancer

DATE-ISSUED: September 17, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Purcell; William P.	Memphis	TN	N/A	N/A
Parish, Jr.; Harlie A.	Memphis	TN	N/A	N/A

APPL-NO: 07/ 609609

DATE FILED: November 6, 1990

PARENT-CASE:

CROSS REFERENCE TO A RELATED APPLICATION This is a divisional of co-pending application Ser. No. 284,185, filed on Dec. 14, 1988, now U.S. Pat. No. 4,994,491.

US-CL-CURRENT: 514/529; 514/354 ; 514/355 ; 514/423 ; 514/425 ; 514/448 ; 514/461 ; 514/512 ; 514/522 ; 514/547 ; 514/548 ; 514/549 ; 514/725

ABSTRACT:

The dermal use of non-irritating retinoids such as the esters and amides of 13-cis and 13-trans-retinoic acid for effecting the reduction and reversal of photoaging and skin cancer is disclosed.

5 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Detailed Description Text - DETX:

The ODC/Retinoid Bioassay is based on the method of Verma, A. K. and Boutwell, R. K., Cancer Res. (1977) 37:2196-2201. The ODC assay measures a compound's effect on the prevention of the induction of ODC, namely the effect of the retinoid compound on the inhibition of the tumor **promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) induced** ODC activity. The assay was carried out using CD-1 mice (aged 7 to 9 weeks). The dorsal hair of the mice was shaved 3-4 days before testing. Four mice were used for each point. The test retinoids, at one of two dose levels (1.7 and 17 nmoles) dissolved in 0.2

ml of acetone was applied topically to the back of each shaved mouse. A single dose of TPA (17 nM) was applied to the back of each treated mouse 30 minutes later. Control groups were treated with either acetone alone, TPA, or tretinoin. The mice were killed by cervical dislocation 5 hours after TPA treatment.

US-PAT-NO: 4994491

DOCUMENT-IDENTIFIER: US 4994491 A

TITLE: Dermal uses of trans-retinoids for the treatment of cancer

DATE-ISSUED: February 19, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Purcell; William P.	Memphis	TN	N/A	N/A
Parish, Jr.; Harlie A.	Memphis	TN	N/A	N/A

APPL-NO: 07/ 284185

DATE FILED: December 14, 1988

US-CL-CURRENT: 514/529; 514/354 ; 514/355 ; 514/423 ; 514/425 ; 514/448 ; 514/461 ; 514/512 ; 514/522 ; 514/547 ; 514/548 ; 514/549

ABSTRACT:

The dermal use of non-irritating retinoids such as the esters and amides of 13-cis and 13-trans-retinoic acid for effecting the reduction and reversal of photoaging and skin cancer is disclosed.

5 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Detailed Description Text - DETX:

The ODC/Retinoid Bioassay is based on the method of Verma, A. K. and Boutwell, R. K., Cancer Res. (1977) 37:2196-2201. The ODC assay measures a compound's effect on the prevention of the induction of ODC, namely the effect of the retinoid compound on the inhibition of the tumor **promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) induced** ODC activity. The assay was carried out using CD-1 mice (aged 7 to 9 weeks). The dorsal hair of the mice was shaved 3-4 days before testing. Four mice were used for each point. The test retinoids, at one of two dose levels (1.7 and 17 nmoles) dissolved in 0.2 ml of acetone was applied topically to the back of each shaved mouse. A single dose of TPA (17 nM) was applied to the back of each treated mouse 30 minutes later. Control groups were treated with either acetone alone, TPA, or tretinoin. The mice were killed by cervical dislocation 5 hours after TPA treatment.

US-PAT-NO: 4923818

DOCUMENT-IDENTIFIER: US 4923818 A

TITLE: DNA clone of human type IV collagenase

DATE-ISSUED: May 8, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Goldberg; Gregory I.	St. Louis	MO	N/A	N/A
Eisen; Arthur Z.	St. Louis	MO	N/A	N/A

APPL-NO: 07/ 352069

DATE FILED: May 15, 1989

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION This is a continuation-in-part of copending application Ser. No. 07/93,421, filed Sept, 4, 1987.

US-CL-CURRENT: 435/226; 435/320.1 ; 536/23.2 ; 536/23.5

ABSTRACT:

The cDNA clone representing the full size human type IV collagenase (gelatinase) is disclosed.

5 Claims, 9 Drawing figures

Exemplary Claim Number: 5

Number of Drawing Sheets: 14

---------- KWIC ---------

Brief Summary Text - BSTX:

The gelatinase protein sequence consists of three domains, an amino terminal domain, I, of 192 amino acids, a middle domain, II, of 175 amino acids, and a carboxy terminal domain, III, of 264 amino acids. The outer domains I and II show homology to collagenase described in U.S. Pat. No. 4,772,557, the disclosure of which is incorporated herein by reference, and to stromelysin described by Wilhelm et al., Proc. Natl. Acad. Sci. USA, 84, 6725-6729 (1987). The middle domain II, 175 amino acids long, is organized into three 58 amino acid long head-to-tail repeats which show homology to the type II motif of the collagen binding domain of fibronectin. In contrast to the expression

of human fibroblast collagenase and stromelysin, the expression of type IV collagenase (gelatinase) by a variety of human fibroblast cell strains is not **modulated by the tumor promoter TPA (12-0-tetradecanolphorbol 13-acetate**).

US-PAT-NO: 4708964

DOCUMENT-IDENTIFIER: US 4708964 A

TITLE: Lipoxygenase inhibitors

DATE-ISSUED: November 24, 1987

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Allen; Larry M.	Fort Collins	CO	N/A	N/A

APPL-NO: 06/ 578414

DATE FILED: February 9, 1984

US-CL-CURRENT: 514/533; 514/23 ; 514/464 ; 514/469 ; 514/532 ; 514/559 ; 514/570 ; 514/64 ; 514/718 ; 514/731 ; 514/826 ; 514/830 ; 514/859 ; 514/863

ABSTRACT:

This invention provides methods of using a number of compounds for the inhibition of lipoxygenase in humans. Pathological conditions which may be treated by the compounds described herein include psoriasis, cellular proliferation, skin allergies, insect bites, allergic rhinitis, conjunctivitis, hay fever, bronchial asthma, allergic gastroenteritis, uterine contractions, hyperactivity of the colon and bronchospasms.

6 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Other Reference Publication - OREF:

Satoshi Yamamoto, et al., "Turmor **Promoter 12-O-Tetradecanoylphorbol-13-Acetate-Induced** Insulin Secretion: Inhibition by Phospholipase A.sub.2 -And Lipoxygenase-Inhibitors", Biochemical and Biophysical Research Communications, vol. 105, No. 2, pp. 759-765, Mar. 30, 1982.

US-PAT-NO: 4169099

DOCUMENT-IDENTIFIER: US 4169099 A

TITLE: Catalyst and process for producing ethylene oxide

DATE-ISSUED: September 25, 1979

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Khoobiar; Sargis	Kinnelon	NJ	N/A	N/A

APPL-NO: 05/ 909327

DATE FILED: May 25, 1978

US-CL-CURRENT: 549/536; 502/348

ABSTRACT:

In the oxidation of ethylene with molecular oxygen, improved selectivity to the production of ethylene oxide is obtained by employing a silver catalyst containing greater than zero and up to about 300 ppm by weight of thallium, based on the total catalyst.

8 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX:

After the particles have been dried, it is an important part of the preparation process to activate the particles by heating to decompose the silver compound or complex and to reduce the resulting silver oxide in order to produce an active catalyst. The **promoter metal compounds, such as thallium acetate, are also decomposed during the activation** process. It is common practice to heat the particles gradually in the presence of air to temperatures in the range of 200.degree.-300.degree. C. or more and to retain that temperature until the activation is complete. After the catalysts have been activated, they may be used for the oxidation of ethylene to ethylene oxide.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2002/10/29 12:02
2	L2	302653	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2002/10/29 12:03
3	L3	63566	promoter$1	USPAT; US-PGPUB	2002/10/29 12:03
4	L4	1256081	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2002/10/29 12:03
5	L5	49	2 near10 4 near10 3	USPAT; US-PGPUB	2002/10/29 12:04
6	L6	7894	pps or phosphoenol adj pyruvate adj synthase1	USPAT; US-PGPUB	2002/10/29 12:06
7	L7	7896	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2002/10/29 12:06
8	L8	75	7 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2002/10/29 12:07
9	L9	15	8 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2002/10/29 12:08

PGPUB-DOCUMENT-NUMBER: 20020155521

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020155521 A1

TITLE: APPLICATION OF GLUCOSE TRANSPORT MUTANTS FOR PRODUCTION OF AROMATIC
PATHWAY COMPOUNDS

PUBLICATION-DATE: October 24, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
VALLE, FERNANDO	CUERNAVACA	CA	MX	
MEJIA, NOEMI	CUERNAVACA		MX	
BERRY, ALAN	BELMONT		US	

APPL-NO: 08/ 940692

DATE FILED: September 30, 1997

CONTINUED PROSECUTION APPLICATION: This is a publication of a continued prosecution application (CPA) filed under 37 CFR 1.53(d).

RELATED-US-APPL-DATA:

child 08940692 A1 19970930 parent continuation-of 08435510 19950505 US ABANDONED

US-CL-CURRENT: 435/41,435/108 ,435/243 ,435/252.1 ,435/252.3 ,435/252.33 ,435/252.8 ,435/440 ,435/471

ABSTRACT:

This invention describes methods for enhancing carbon flow into a pathway of a host cell to enhance the biosynthetic production of compounds therefrom, the host cells being selected based on being phenotypically Pts.sup.-/glucose.sup.+. Such host cells are capable of transporting glucose without consuming PEP, resulting in conservation of PEP which can be re-directed into the pathway in order to enhance the production of desired compounds along the pathway. Pts.sup.-/glucose.sup.+ mutants have been shown to be advantageous for the enhanced production of the aromatic amino acids.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX:

[0004] Phosphoenolpyruvate (PEP) is one of the major building blocks that cells use in their biosynthetic routes, particularly in amino acid biosynthesis (see FIG. 1). For example, the synthesis of one molecule of chorismate (the common precursor to all of the aromatic amino acids) requires two molecules of PEP. To date, approaches taken to **increase** the influx of carbon sources into and through the common aromatic pathway typically relate to **increasing** the PEP supply in the cell by eliminating pyruvate kinase (pyk mutants) [1] and/or eliminating PEP carboxylase (ppc mutants) [2]. A third approach to **increasing** the PEP supply in the cell is to **amplify** the expression of the **pps gene** (encoding PEP synthase, which converts pyruvate to PEP) (U.S. Ser. No. 08/307,371, the disclosure of which is incorporated herein by reference). Additional approaches to **increase** the flux of carbon into and through the common aromatic pathway relate to **increasing** the intracellular supply of D-erythrose 4-phosphate (E4P), the other necessary precursor (with PEP) for aromatic biosynthesis. This approach may utilize **overexpression** of a transketolase gene (tktA or tktB), the product of which (transketolase) catalyzes the conversion of D-fructose 6-phosphate to E4P (U.S. Pat. No. 5,168,056, the disclosure of which is incorporated herein by reference). Another approach to **increasing** E4P availability may utilize **overexpression** of the transaldolase gene (talA) which encodes the enzyme transaldolase [3], which catalyzes the conversion of D-sedoheptulose 7-phosphate plus glyceraldehyde 3-phosphate to E4P plus fructose 6-phosphate.

Summary of Invention Paragraph - BSTX:

[0011] In another embodiment there is provided a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway of said host cell, the method comprising the step of culturing under suitable conditions a phenotypically Pts.sup.-/glucose.sup.+ host cell. The host cell may preferably be transformed with recombinant DNA containing the tktA, tktB, talA or **pps genes** such that the products of these genes are expressed at enhanced levels relative to wild-type host cells. Alternatively, **increased** levels of such gene products can be achieved by chromosomal mutation or chromosomal integration by methods available to the skilled artisan. Chromosomal mutations include mutations in the tktA, tktB, talA or **pps genes** themselves, or in the promoters or regulatory genes controlling their expression. In yet another embodiment of the invention relating to the overproduction of desired compounds, the host cell may further comprise additional recombinant DNA containing one or more gene(s) coding for enzymes catalyzing reactions in the common aromatic pathway of the host cell. As for tktA, tktB, talA or **pps, increased expression of gene**(s) encoding the enzymes of the common aromatic pathway may be effected by mutating the genes themselves, or the promoters or regulatory genes governing their expression. The host cells can be transformed with a wide variety of genes from a given pathway, depending on the desired product to be made by the cells upon fermentation.

PGPUB-DOCUMENT-NUMBER: 20020137204

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020137204 A1

TITLE: Techniques for growth and differentiation of human pluripotent stem cells

PUBLICATION-DATE: September 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carpenter, Melissa K.	Castro Valley	CA	US	
Funk, Walter D.	Hayward	CA	US	
Gold, Joseph D.	San Francisco	CA	US	
Inokuma, Margaret S.	San Jose	CA	US	
Xu, Chunhui	Cupertino	CA	US	

APPL-NO: 10/ 039956

DATE FILED: October 23, 2001

RELATED-US-APPL-DATA:

child 10039956 A1 20011023 parent continuation-of 09859291 20010516 US PENDING
non-provisional-of-provisional 60175581 20000111 US
non-provisional-of-provisional 60213740 20000622 US
non-provisional-of-provisional 60213739 20000622 US
non-provisional-of-provisional 60216387 20000707 US
non-provisional-of-provisional 60220064 20000721 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
US	PCT/US01/01030	2001US-PCT/US01/01030	January 10, 2001

US-CL-CURRENT: 435/366

ABSTRACT:

This disclosure provides an improved system for culturing human pluripotent stem (pPS) cells in the absence of feeder cells. The role of the feeder cells can be replaced by supporting the culture on an extracellular matrix, and culturing the cells in a conditioned medium. Permanent cell lines are provided that can produce conditioned medium on a commercial scale. Methods have also been discovered to genetically alter pPS cells by introducing the cells with a viral vector or DNA/lipid complex. The system described in this disclosure allows for bulk proliferation of pPS cells for use in studying the biology of pPS cell differentiation, and the production of important products for use in human therapy.

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Ser. No. 09/859,291, filed May 16, 2001, and claims priority to the following patent applications: U.S. Ser. No. 60/175,581, filed Jan. 11, 2000; U.S. Ser. No. 60/213,740, filed Jun. 22, 2000; U.S. Ser No. 60/213,739, filed Jun. 22, 2000; U.S. Ser. No. 60/216,387, filed Jul. 7, 2000; U.S. Ser. No. 60/220,064, filed Jul. 21, 2000; U.S. Ser. No. 09/688,031, filed Oct. 10, 2000; and PCT/US01/01030, (designating the U.S.) filed Jan. 10, 2001, and published as WO 01/51616 on Jul. 19, 2001.

[0002] The priority applications are hereby incorporated herein by reference in their entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX:

[0164] Of particular interest are libraries optimized for expression of the cDNA in pluripotent stem cells. Methylation patterns and other regulatory control mechanisms in embryonic cells can suppress transcription of genes under control of promoters such as CMV, which are active in most other eukaryotic cell types. It has been discovered that promoters for house-keeping **genes active in pPS** cells may be effective for controlling transcription of artificially introduced encoding regions. As illustrated in Example 14, an appropriate promoter can be selected experimentally using reporter constructs comprising test promoter sequences, a reporter gene such as green fluorescent protein or .beta.-galactosidase, and a drug resistance gene. An appropriate promoter will have the characteristic of causing expression of the reporter gene, without substantially **increasing** the proportion of cells lost to differentiation. Using this selection strategy, the promoter for PGK, EF1.alpha., and UbiC have been determined as effective for construction of libraries expressible in pPS cells.

Detail Description Paragraph - DETX:

[0175] The **sequence data of an mRNA or cDNA from pPS** cells can also be used to manufacture peptides that comprise a sequence contained in an encoding region. Amino acid sequences can be modified to remove or add segments, or introduce mutations and other changes for any desirable purpose. Substantially identical polypeptides or polypeptide fragments share an epitope recognized by an antibody specific for a protein encoded in a cDNA of an expression library from pPS cells or their differentiated progeny, in preference to other nucleotide sequences contained in the human genome or expressed in other cell types. In certain embodiments, the peptides are 60%, 80%, 90%, 95%, or 100% identical to a peptide or peptide fragment encoded in the mRNA or cDNA, in order of **increasing** preference. The length of the identical or homologous sequence compared with the prototype polypeptide can be about 7,10, 15, 25, 50 or 100 residues in order of **increasing** preference, up to the length of the entire protein.

Detail Description Paragraph - DETX:

[0179] Polynucleotides, polypeptides, and antibody derived from sequence data obtained from mRNA or cDNA of this invention have a number of important commercial applications. For example, **genes or proteins that are expressed in pPS** cells but decrease during differentiation can be used as molecular markers of the undifferentiated state. Reagents corresponding to these markers, such as antibodies, can be used to eliminate undifferentiated pPS cells from a population of differentiated cells by immunoaffinity isolation or complement-mediated lysis. Genes or proteins that **increase** expression levels during differentiation can be used in a similar manner to purify, enrich, remove or eliminate specific cell types derived from pPS cells. These markers may serve as indicators of broad classes of cell differentiation, such as genes or proteins expressed in mesodermal, endodermal or ectodermal lineages, or may serve as specific markers of a confined spectrum of highly differentiated cell types.

PGPUB-DOCUMENT-NUMBER: 20020090723

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020090723 A1

TITLE: Techniques for growth and differentiation of human pluripotent stem cells

PUBLICATION-DATE: July 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carpenter, Melissa K.	Castro Valley	CA	US	
Inokuma, Margaret S.	San Jose	CA	US	
Xu, Chunhui	Cupertino	CA	US	

APPL-NO: 09/ 994440

DATE FILED: November 26, 2001

RELATED-US-APPL-DATA:

child 09994440 A1 20011126 parent continuation-of 09859291 20010516 US PENDING
non-provisional-of-provisional 60175581 20000111 US
non-provisional-of-provisional 60213740 20000622 US
non-provisional-of-provisional 60213739 20000622 US
non-provisional-of-provisional 60216387 20000707 US
non-provisional-of-provisional 60220064 20000721 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
US	PCT/US01/01030	2001US-PCT/US01/01030	January 10, 2001
WO	01/51616	2001WO-01/51616	July 19, 2001

US-CL-CURRENT: 435/366,435/368

ABSTRACT:

This disclosure provides an improved system for culturing human pluripotent stem (pPS) cells in the absence of feeder cells. The role of the feeder cells can be replaced by supporting the culture on an extracellular matrix, and culturing the cells in a conditioned medium. Permanent cell lines are provided that can produce conditioned medium on a commercial scale. Methods have also been discovered to genetically alter pPS cells by introducing the cells with a viral vector or DNA/lipid complex. The system described in this disclosure allows for bulk proliferation of pPS cells for use in studying the biology of pPS cell differentiation, and the production of important products for use in human therapy.

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Ser. No. 09/859,291, filed May 16, 2001, and claims priority to the following patent applications: U.S. Ser. No. 60/175,581, filed Jan. 11, 2000; U.S. Ser. No. 60/213,740, filed Jun. 22, 2000; U.S. Ser. No. 60/213,739, filed Jun. 22, 2000; U.S. Ser. No. 60/216,387, filed Jul. 7, 2000; U.S. Ser. No. 60/220,064, filed Jul.21, 2000; U.S. Ser. No. 09/688,031, filed Oct. 10, 2000; and PCT/US01/01030, (designating the U.S.) filed Jan. 10, 2001, and published as WO 01/51616 on Jul. 19, 2001.
[0002] The priority applications are hereby incorporated herein by reference in their entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX:

[0181] Of particular interest are libraries optimized for expression of the cDNA in pluripotent stem cells. Methylation patterns and other regulatory control mechanisms in embryonic cells can suppress transcription of genes under control of promoters such as CMV, which are active in most other eukaryotic cell types. It has been discovered that promoters for house-keeping **genes active in pPS** cells may be effective for controlling transcription of artificially introduced encoding regions. As illustrated in Example 14, an appropriate promoter can be selected experimentally using reporter constructs comprising test promoter sequences, a reporter gene such as green fluorescent protein or .beta.-galactosidase, and a drug resistance gene. An appropriate promoter will have the characteristic of causing expression of the reporter gene, without substantially **increasing** the proportion of cells lost to differentiation. Using this selection strategy, the promoter for PGK, EF1.alpha., and UbiC have been determined as effective for construction of libraries expressible in pPS cells.

Detail Description Paragraph - DETX:

[0194] The **sequence data of an mRNA or cDNA from pPS** cells can also be used to manufacture peptides that comprise a sequence contained in an encoding region. Amino acid sequences can be modified to remove or add segments, or introduce mutations and other changes for any desirable purpose. Substantially identical polypeptides or polypeptide fragments share an epitope recognized by an antibody specific for a protein encoded in a cDNA of an expression library from pPS cells or their differentiated progeny, in preference to other nucleotide sequences contained in the human genome or expressed in other cell types. In certain embodiments, the peptides are 60%, 80%, 90%, 95%, or 100% identical to a peptide or peptide fragment encoded in the mRNA or cDNA, in order of **increasing** preference. The length of the identical or homologous sequence compared with the prototype polypeptide can be about 7, 10, 15, 25, 50 or 100 residues in order of **increasing** preference, up to the length of the entire protein.

Detail Description Paragraph - DETX:

[0198] Polynucleotides, polypeptides, and antibody derived from sequence data obtained from mRNA or cDNA of this invention have a number of important commercial applications. For example, **genes or proteins that are expressed in pPS** cells but decrease during differentiation can be used as molecular markers of the undifferentiated state. Reagents corresponding to these markers, such as antibodies, can be used to eliminate undifferentiated pPS cells from a population of differentiated cells by immunoaffinity isolation or complement-mediated lysis. Genes or proteins that **increase** expression levels during differentiation can be used in a similar manner to purify, enrich, remove or eliminate specific cell types derived from pPS cells. These markers may serve as indicators of broad classes of cell differentiation, such as genes or proteins expressed in mesodermal, endodermal or ectodermal lineages, or may serve as specific markers of a confined spectrum of highly differentiated cell types.

PGPUB-DOCUMENT-NUMBER: 20020081724

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020081724 A1

TITLE: Techniques for growth and differentiation of human pluripotent stem cells

PUBLICATION-DATE: June 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carpenter, Melissa K.	Castro Valley	CA	US	
Funk, Walter D.	Hayward	CA	US	
Gold, Joseph D.	San Francisco	CA	US	
Inokuma, Margaret S.	San Jose	CA	US	
Xu, Chunhui	Cupertino	CA	US	

APPL-NO: 09/ 859291

DATE FILED: May 16, 2001

RELATED-US-APPL-DATA:

child 09859291 A1 20010516 parent continuation-of PCT/US01/01030 20010110 US
UNKNOWN non-provisional-of-provisional 60175581 20000111 US
non-provisional-of-provisional 60213740 20000622 US
non-provisional-of-provisional 60213739 20000622 US
non-provisional-of-provisional 60216387 20000707 US
non-provisional-of-provisional 60220064 20000721 US

US-CL-CURRENT: 435/366,435/354 ,435/384

ABSTRACT:

This disclosure provides an improved system for culturing human pluripotent stem (pPS) cells in the absence of feeder cells. The role of the feeder cells can be replaced by supporting the culture on an extracellular matrix, and culturing the cells in a conditioned medium. Permanent cell lines are provided that can produce conditioned medium on a commercial scale. Methods have also been discovered to genetically alter pPS cells by introducing the cells with a viral vector or DNA/lipid complex. The system described in this disclosure allows for bulk proliferation of pPS cells for use in studying the biology of pPS cell differentiation, and the production of important products for use in human therapy.

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to the following pending U.S. patent

applications: U.S. Ser. No. 60/175,581, filed Jan. 11, 2000; U.S. Ser. No. 60/213,740, filed Jun. 22, 2000; U.S. Ser. No. 60/213,739, filed Jun. 22, 2000; U.S. Ser. No. 60/216,387, filed Jul. 7, 2000; U.S. Ser. No. 60/220,064, filed Jul. 21, 2000; and U.S. Ser. No. 09/688,031, filed Oct. 10, 2000.
[0002] For purposes of prosecution in the U.S., the priority applications are hereby incorporated herein by reference in their entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX:

[0178] Of particular interest are libraries optimized for expression of the cDNA in pluripotent stem cells. Methylation patterns and other regulatory control mechanisms in embryonic cells can suppress transcription of genes under control of promoters such as CMV, which are active in most other eukaryotic cell types. It has been discovered that promoters for house-keeping **genes active in pPS** cells may be effective for controlling transcription of artificially introduced encoding regions. As illustrated in Example 14, an appropriate promoter can be selected experimentally using reporter constructs comprising test promoter sequences, a reporter gene such as green fluorescent protein or .beta.-galactosidase, and a drug resistance gene. An appropriate promoter will have the characteristic of causing expression of the reporter gene, without substantially **increasing** the proportion of cells lost to differentiation. Using this selection strategy, the promoter for PGK, EF1.alpha., and UbiC have been determined as effective for construction of libraries expressible in pPS cells.

Detail Description Paragraph - DETX:

[0191] The **sequence data of an mRNA or cDNA from pPS** cells can also be used to manufacture peptides that comprise a sequence contained in an encoding region. Amino acid sequences can be modified to remove or add segments, or introduce mutations and other changes for any desirable purpose. Substantially identical polypeptides or polypeptide fragments share an epitope recognized by an antibody specific for a protein encoded in a cDNA of an expression library from pPS cells or their differentiated progeny, in preference to other nucleotide sequences contained in the human genome or expressed in other cell types. In certain embodiments, the peptides are 60%, 80%, 90%, 95%, or 100% identical to a peptide or peptide fragment encoded in the mRNA or cDNA, in order of **increasing** preference. The length of the identical or homologous sequence compared with the prototype polypeptide can be about 7, 10, 15, 25, 50 or 100 residues in order of **increasing** preference, up to the length of the entire protein.

Detail Description Paragraph - DETX:

[0195] Polynucleotides, polypeptides, and antibody derived from sequence data obtained from mRNA or cDNA of this invention have a number of important

commercial applications. For example, **genes or proteins that are expressed in pPS** cells but decrease during differentiation can be used as molecular markers of the undifferentiated state. Reagents corresponding to these markers, such as antibodies, can be used to eliminate undifferentiated pPS cells from a population of differentiated cells by immunoaffinity isolation or complement-mediated lysis. Genes or proteins that **increase** expression levels during differentiation can be used in a similar manner to purify, enrich, remove or eliminate specific cell types derived from pPS cells. These markers may serve as indicators of broad classes of cell differentiation, such as genes or proteins expressed in mesodermal, endodermal or ectodermal lineages, or may serve as specific markers of a confined spectrum of highly differentiated cell types.

US-PAT-NO: 6472169

DOCUMENT-IDENTIFIER: US 6472169 B1

TITLE: Biocatalytic synthesis of shikimic acid

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Frost; John W.	Okemos	MI	N/A	N/A
Frost; Karen M.	Okemos	MI	N/A	N/A
Knop; David R.	Okemos	MI	N/A	N/A

APPL-NO: 09/ 676609

DATE FILED: September 30, 2000

PARENT-CASE:

This application is a continuation-in-part of Ser. No. 09/240,440 filed Jan. 29, 1999.

US-CL-CURRENT: 435/41; 435/127 ; 435/156 ; 435/189 ; 435/193 ; 435/232 ; 435/252.3 ; 435/320.1 ; 435/822 ; 435/849 ; 435/911 ; 435/940 ; 536/23.2

ABSTRACT:

A bioengineered synthesis scheme for the production of shikimic acid from a carbon source is provided. Methods of producing shikimic acid from a carbon source based on the synthesis scheme are also provided.

21 Claims, 13 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

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Detailed Description Text - DETX:

In a further embodiment, the E. coli comprises plasmid pKD15.071B. This plasmid is derived from and carries the same **gene inserts as pKD12.138 as well as a pps gene** insert encoding for phosphoenolpyruvate (PEP) synthase. PEP synthase catalyzes the conversion of pyruvate back to PEP. Elevated expression of PEP synthase along with transketolase provides an **increase** in the amount of shikimic acid produced.

US-PAT-NO: 6319696

DOCUMENT-IDENTIFIER: US 6319696 B1

TITLE: Process for producing L-amino acids

DATE-ISSUED: November 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kishino; Hiroko	Kawasaki	N/A	N/A	JP
Izui; Masako	Kawasaki	N/A	N/A	JP
Ono; Yukiko	Kawasaki	N/A	N/A	JP
Ito; Hisao	Kawasaki	N/A	N/A	JP
Kurahashi; Osamu	Kawasaki	N/A	N/A	JP

APPL-NO: 09/ 011762

DATE FILED: April 17, 1998

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	7-221561	August 30, 1995
JP	8-200860	July 30, 1996

PCT-DATA:
APPL-NO: PCT/JP96/02399
DATE-FILED: August 27, 1996
PUB-NO: WO97/08333
PUB-DATE: Mar 6, 1997
371-DATE: Apr 17, 1998
102(E)-DATE: Apr 17, 1998

US-CL-CURRENT: 435/115; 435/116

ABSTRACT:

A microorganism, which has an ability to produce L-amino acid, especially L-phenylalanine, L-tryptophane, L-tyrosine, L-threonine, or L-isoleucine, in which a phosphoenolpyruvate-producing ability is enhanced, is cultivated in a medium so that the L-amino acid is produced and accumulated in the medium to collect the L-amino acid.

6 Claims, 4 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 4

---------- KWIC ---------

Brief Summary Text - BSTX:

Phosphoenolpyruvate synthase (hereinafter abbreviated as "PPS" is an enzyme which is broadly found in the microorganism. This enzyme plays an important role to supply PEP from pyruvic acid in glyconeogenesis. Escherichia coli, which is a bacterium belonging to the genus Escherichia, has been used to perform cloning of a **gene (pps)** coding for **PPS, determination of the nucleotide sequence** of the gene, and functional analysis for the enzyme. Besides, it has been reported that DAHP is produced at a value approximate to the theoretical yield by means of simultaneous **amplification of the pps gene** and the transketorase gene in a dehydroquinate synthase-deficient strain (Patnaik, R. et al., Appl. Environ. Mircobiol., Vol. 60, No. 11, 3903-3908 (1994)). However, there has been known no case in which **amplification of the pps gene** enhances the productivity of aromatic amino acids and other amino acids.

Brief Summary Text - BSTX:

A means for enhancing the phosphoenolpyruvate-producing ability of the microorganism is, for example, to enhance an activity of PPS in microbial cells. Means for enhancing the activity of PPS in the microbial cells include, for example, a method to **increase** an amount of expression of a **pps gene** in the microbial cells, as well as a method to introduce, into the cells, a **gene cording for PPS** having a high specific activity.

Brief Summary Text - BSTX:

Specifically, means for **increasing** the amount of expression of the **pps gene** in the microbial cells include, for example, a method to **increase** a copy number of the **pps gene** in the microbial cells, as well as a method to enhance a transcriptive activity of a promoter for the **pps gene**.

Brief Summary Text - BSTX:

The microorganism preferably used in the present invention is not specifically limited, and it includes, for example, microorganisms belonging to the genera Escherichia, Brevibacterium, Corynebacterium, Bacillus, Serratia, and Pseudomonas, provided that a DNA fragment containing a replication origin of a plasmid is obtained for the microorganism, the **pps gene** functions in the microorganism, the copy number of the **pps gene** can be **increased** in the microorganism, and the microorganism has the L-amino acid-producing ability (for example, in the case of L-phenylalanine, those acquired the L-phenylalanine-producing ability by conferring, for example, resistance to L-phenylalanine analog). Among them, those preferably used are bacteria belonging to the genus Escherichia and the coryneform bacteria.

Brief Summary Text - BSTX:

The means for enhancing the PPS activity includes the **increase** of the amount of expression of the **pps gene** in the microbial cells. One of the means for enhancing the **PPS activity is to modify the pps gene to create PPS** having enhanced activity.

Brief Summary Text - BSTX:

The means for **increasing** the amount of expression of the **pps gene** in the microbial cells includes the **increase** of the copy number of the **pps gene** in the microbial cells. In order to **increase** the copy number of the **pps gene,** it is necessary to obtain a DNA fragment containing the same gene. The **pps gene** has been cloned in Escherichia coli as a bacterium belonging to the genus Escherichia, and its nucleotide sequence has been determined (Mol. Gen. Genet., 231, 332 (1992)). Accordingly, the preparation of the DNA fragment containing the same gene is achieved by using a method disclosed in the document described above. A desired DNA fragment can be obtained by using a hybridization method based on the use of a synthetic DNA probe prepared with reference to the nucleotide sequence described above, or by using a PCR (Polymerase Chain Reaction) method based on the use of synthetic DNA primers prepared with reference to the same nucleotide sequence. The copy number of the **pps gene** can be **increased** by ligating the DNA fragment containing the **pps gene** with a vector DNA autonomously replicable in a target microorganism, and introducing an obtained recombinant DNA fragment into the same microorganism.

Brief Summary Text - BSTX:

are suitable, which make it possible to **amplify** a region of about 3.3 kb containing the **pps gene**. These primers make it possible to **amplify the pps gene** in a form of having SalI cleavage ends at both terminals. When the restriction enzyme cleavage ends are introduced into the terminals of the PCR product, then the **amplified** DNA fragment is conveniently cloned by using the corresponding restriction enzyme, and the DNA fragment is conveniently transferred to another vector DNA. The primer DNA's can be synthesized, for example, by using a DNA synthesizer model 380B produced by Applied Biosystems in accordance with the phosphoamidite method (see Tetrahedron Letters, 22, 1859 (1981)). The PCR reaction can be performed, for example, by using DNA Thermal Cycler PJ2000 Type produced by Takara Shuzo and using Taq DNA polymerase in accordance with the method designated by the supplier.

Brief Summary Text - BSTX:

When the **pps gene amplified** in accordance with the PCR method is introduced into a bacterium belonging to the genus Escherichia, then it is ligated with vector DNA autonomously replicable in cells of the bacterium belonging to the genus Escherichia, and obtained recombinant DNA is introduced into cells of the bacterium belonging to the genus Escherichia.

Brief Summary Text - BSTX:

Plasmid vector DNA is preferably used as the vector DNA to be used in the present invention. When the microorganism into which the gene is introduced is Escherichia coli, those usable as the vector DNA include, for example, pTWV228, pUC19, pUC18, pBR322, pHSG299, pHSG399, and RSF1010. Besides, vectors composed of phage DNA may be utilized. In order to achieve efficient expression of PPS, it is also preferable to use a promoter which functions in the microorganism, such as lac, trp, and P.sub.L. In order to **increase** the copy number of the **pps gene,** it is also preferable to incorporate DNA containing the **pps gene** into the chromosome in accordance with the method based on the use of transposon (Berg, D. E. and Berg, C. M., Bio/Technol., 1, 417 (1983)), Mu phage (Japanese Laid-Open Patent Publication No. 2-109985), or homologous recombination (Experiments in Molecular Genetics, Cold Spring Harbor Lab. (1972)).

Detailed Description Text - DETX:

Chromosomal DNA was extracted from W3110 strain originating from Escherichia coli K-12 in accordance with the method of Saito and Miura (Biochem. Biophys. Acta, 72, 619 (1963)). On the other hand, oligonucleotide primers to be used for **amplifying the pps gene** from the chromosomal DNA in accordance with the PCR method were synthesized on the basis of a known nucleotide **sequence of the pps gene** (Mol. Gen. Genet., 231, 332 (1992)).

US-PAT-NO: 6172279

DOCUMENT-IDENTIFIER: US 6172279 B1

TITLE: Plant gene construct encoding a protein capable of disrupting the biogenesis of viable pollen

DATE-ISSUED: January 9, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bridges; Ian George	Slater	IA	N/A	N/A
Bright; Simon William	Bucks	N/A	N/A	GB
Jonathan	Maidenhead	N/A	N/A	GB
Greenland; Andrew James	Crowthorne	N/A	N/A	GB
Schuch; Wolfgang Walter				

APPL-NO: 08/ 554811

DATE FILED: November 7, 1995

PARENT-CASE:

This is a continuation of application Ser. No. 08/293,422, filed Aug. 22, 1994, now U.S. Pat. No. 5,808,034, which is a continuation of Ser. No. 08/165,544 filed Dec. 13, 1993, now abandoned, which is a continuation of Ser. No. 07/824,883 filed Jan. 22, 1992, now abandoned which is a continuation of Ser. No. 07/470,654 filed Jan. 26, 1990, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	8901677	January 26, 1989

US-CL-CURRENT: 800/274; 536/23.5 ; 536/23.6 ; 536/23.7 ; 536/24.1 ; 800/268 ; 800/271 ; 800/303 ; 800/320.1

ABSTRACT:

Male sterility is imparted to a plant by a cascade of gene sequences which expresses a protein which disrupts the biosynthesis of viable pollen. Expression of the disrupter protein is restricted to male parts of the plant by an upstream promoter sequence which is specific to male flowers, the male specific promoter being under control of an operator sequence. The cascade also includes a gene encoding a repressor protein specific for that operator. Expression of the repressor protein is under control of a chemically inducible promoter which is inducible by the application to the plant by, spraying or like process, of an exogenous chemical. In the absence of the exogenous chemical inducer, no repressor protein is expressed, resulting in expression of the disrupter protein and, consequently, male sterility. Fertility may be restored to the plant, when required for maintenance of the line, by spraying

with the inducer, resulting in expression of the repressor which binds the operator and inhibits expression of the disrupter protein.

25 Claims, 39 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 44

---------- KWIC ---------

Detailed Description Text - DETX:

Initial experiments showed that 500 .mu.g/ml TPNPG was only able to retard the growth of lac.sup.+ cells, allowing the formation of small blue colonies after 48h at 28.degree. C. However, this background was eliminated in the presence of 1 mg/ml TPNPG, resulting in none of the lac+ cells plated (up to 7.times.10.sup.-7) being able to form blue colonies (Table V). In contrast, this TPNPG concentration did not noticeably affect the viability of the lac cells. This demonstrates the high selective power of TPNPG againstlac.sup.+ cells, even when the lacY gene is chromosomal and thus at a low copy number. In this respect, the higher copy number and therefore **increased** expression level of the lac **genes on the pPS** plasmids should result in a greater waste of energy on TPNPG uptake, making the killing of lac.sup.+ cells more effective.

US-PAT-NO: 6010887

DOCUMENT-IDENTIFIER: US 6010887 A

TITLE: Regulation of gene expression

DATE-ISSUED: January 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bridges; Ian George	Slater	IA	N/A	N/A
Bright; Simon William	Bucks	N/A	N/A	GB
Jonathan	Maidenhead	N/A	N/A	GB
Greenland; Andrew James	Berks	N/A	N/A	GB
Schuch; Wolfgang Walter	Loughbrough	N/A	N/A	GB
Merryweather; Andrew	Limm	N/A	N/A	GB
Pioli; David				

APPL-NO: 08/ 305741

DATE FILED: September 14, 1994

PARENT-CASE:

This is a continuation of application Ser. No. 08/025,803, filed on Mar. 3, 1993 now abandoned, which in turn is a continuation of application Ser. No. 07/470,653, filed Jan. 26, 1990, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	8901676	January 26, 1989

US-CL-CURRENT: 435/91.1; 435/320.1 ; 435/440 ; 435/468 ; 536/24.1 ; 800/278 ; 800/288 ; 800/295

ABSTRACT:

Pseudo-operator sequences may be located in (or inserted into) plant genomes and utilized to drive expression of foreign genes. These pseudo-operator sequences are nucleotide sequences which are present at a suitable location in a gene at which repressor binding will lead to inhibitation or enhancement of gene expression. The disclosed technique permits the design of altered specificity repressors, which bind the pseudo-operators.

14 Claims, 1 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

---------- KWIC ---------

Detailed Description Text - DETX:

Initial experiments showed that 500 .mu.g/ml TPNPG was only able to retard the growth of lac.sup.+ cells, allowing the formation of small blue colonies after 48 h at 28.degree. C. However, this background was eliminated in the presence of 1 mg/ml TPNPG, resulting in none of the lac.sup.+ cells plated (up to 7.times.10.sup.-7) being able to form blue colonies (Table I). In contrast, this TPNPG concentration did not noticeably affect the viability of the lac.sup.- cells. This demonstrates the high selective power of TPNPG againstlac.sup.+ cells, even when the lacY gene is chromosomal and thus at a low copy number. In this respect, the higher copy number and therefore **increased** expression level of the lac **genes on the pPS** plasmids should result in a greater waste of energy on TPNPG uptake, making the killing of lac.sup.+ cells more effective.

US-PAT-NO: 5985617

DOCUMENT-IDENTIFIER: US 5985617 A

TITLE: Microorganisms and methods for overproduction of DAHP by cloned PPS gene

DATE-ISSUED: November 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liao; James C.	Los Angeles	CA	90024	N/A

APPL-NO: 09/ 277183

DATE FILED: March 26, 1999

PARENT-CASE:

This is a Continuation of U.S. patent application Ser. No. 08/801,454 filed on Feb. 18, 1997 U.S. Pat. No. 5,906,925.

US-CL-CURRENT: 435/72; 435/108 ; 435/200 ; 536/23.7 ; 536/24.1

ABSTRACT:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The **overexpression** of phosphoenol pyruvate synthase **increases** DAHP production to near theoretical yields.

29 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Abstract Text - ABTX:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The **overexpression** of phosphoenol pyruvate synthase **increases** DAHP production to near theoretical yields.

Brief Summary Text - BSTX:

The present invention provides genetically engineered strains of microorganisms that **overexpress the pps gene for increasing** the production of DAHP to near theoretical yields. The present invention also provides genetically engineered strains of microorganisms where at least one of the plasmids pPS341, pPSL706, pPS706, or derivatives thereof is transformed into a microorganism for **increasing** the production of DAHP to near theoretical yields.

Brief Summary Text - BSTX:

The present invention further provides a method for **increasing** carbon flow for the biosynthesis of DAHP in a host cell comprising the steps of transforming into the host cell recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced levels relative to wild type host cells, concentrating the transformed cells through centrifugation, resuspending the cells in a minimal, nutrient lean medium, fermenting the resuspended cells, and isolating DAHP from the medium.

Brief Summary Text - BSTX:

The present invention further provides methods of **increasing** carbon flow into the common aromatic pathway of a host cell comprising the step of transforming the host cell with recombinant DNA comprising a **pps gene so that Pps** is expressed at appropriate point in the metabolic pathways at enhanced levels relative to wild type host cells.

Detailed Description Text - DETX:

The inventor have found that cell lines can be developed that **increase** the carbon flux into DAHP production and achieve near theoretical yields of DAHP by **overexpressing** phosphoenolpyruvate synthase (Pps) in the cell lines. **Overexpression** of Pps can **increase** the final concentration and yield of DAHP by as much as two-fold, to a near theoretical maximum as compared to wild type cell lines. The **overexpression** of Pps is achieved by transforming a cell line with recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced level relative to the wild type cell line and so that the yield of DAHP approaches its theoretical value.

Detailed Description Text - DETX:

Besides the use of the **pps gene,** the present invention also provides for transfer of genetic elements comprising the tkt gene, the gene coding for DAHP synthase (aroF in E. coli), the gene coding for 3-dehydroquinate synthase (aroB in E. coli), or other genes encoding enzymes that catalyze reactions in the common aromatic pathway. Such a cell transformation can be achieved by transferring one or more plasmids that contain genes that code for enzymes that

increase the carbon flux for DAHP synthesis and for subsequent synthesis of other desired cyclic, pre-aromatic, and aromatic metabolites. As a result of this transfer of genetic element(s), more carbon enters and moves through the common aromatic pathway relative to wild type host cells not containing the genetic elements of the present invention.

Detailed Description Text - DETX:

In one embodiment, the present invention comprises a method for **increasing** carbon flow into the common aromatic pathway of a host cell by **increasing** the production of DAHP through the **overexpression** of Pps at the appropriate point in the common aromatic pathway to provide additional PEP at the point where PEP condenses with E4P. **Increasing** carbon flow requires the step of transforming the host cell with recombinant DNA containing a **pps genes so that Pps is overexpressed** at enhanced levels relative to wild type host cells. DAHP is then produced by fermentation of the transformed cell in a nutrient medium which the DAHP can be extracted from the medium on a batch wise or continuous extraction procedure.

Detailed Description Text - DETX:

In another embodiment, the present invention involves the co-**overexpression of a pps gene** and other genes coding for enzymes of the common aromatic pathway where additional genetic material is transformed into the host cell. The genes transferred can include the tkt gene, DAHP synthase gene and DHQ synthase gene (preferably the aroF or aroB genes, respectively). Although the work so far has centered around transforming certain host cell strains of E. coli such as AB2847 aroB, this particular host cell may not be the preferred host cell for the commercial production of DAHP or DAHP metabolites through the **overexpression** of Pps.

Detailed Description Text - DETX:

Another embodiment of the present invention is a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway. This method involves the step of **increasing** expression of Pps in the host cell relative to a wild type host cell. The step of **increasing** expression of Pps can include transferring into the host cell a vector carrying the **pps gene**. The **overexpression** of Pps results in forcing **increased** carbon flow into the biosynthesis of DAHP.

Detailed Description Text - DETX:

In another embodiment of the present invention, a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway relative to wild type host cell's biosynthetic production of such compound is provided. This method requires the step of **increasing** expression in a host cell of a protein catalyzing conversion of pyruvate to PEP. The

expression of such a protein can involve transferring into the host cell recombinant DNA including a **pps gene**.

Detailed Description Text - DETX:

One preferred embodiment of the present invention encompasses modification of a host cell to cause **overexpression** of an enzyme having the catalytic properties of naturally derived Pps, and, thereby maximizing the yield of DAHP to near theoretical yields. Enzymes having the catalytic activity of Pps include, but are not limited to, Pps produced by expression in whole cells of a naturally derived **pps gene,** enzymes produced by expression in whole cells of a naturally derived **pps gene** modified by sequence deletion or addition so that the expressed enzyme has an amino acid **sequence that varies from unmodified Pps,** abzymes produced to have catalytic sites with steric and electronic properties corresponding to catalytic sites of Pps, or other proteins produced to have the capability of catalyzing the conversion of pyruvate to PEP by any other art recognized means.

Detailed Description Text - DETX:

Additionally, the transformation of DNA, including the **pps gene,** into microorganisms engineered for the **overexpression** of other substrates, and/or **overexpression** or derepression of enzymes in the pentose phosphate or common aromatic pathway can be used to tailor the microorganism to achieve near theoretical yields of such DAHP metabolites as tyrosine, tryptophan, phenylalanine, and other aromatic metabolites such as indigo, catechol and quinoid organics such as quinic acid, benzoquinone, and hydroquinone.

Detailed Description Text - DETX:

This example demonstrates that the E. coli AB2847 is unable to utilize DAHP, and accumulates DAHP in the medium if DAHP synthase is **overexpressed**. This strain was used as a host for detecting the flux committed to the aromatic pathways. Since Draths et al. (Draths, K. M., D. L. Pompliano, D. L. Conley, J. W. Frost, A. Berry, G. L. Disbrow, R. J. Staversky, and J. C. Lievense, "Biocatalytic synthesis of aromatics from D-glucose: The role of transketolase," J. Am. Chem. Soc., 1992, 114, 3956-3962) have shown a possible limitation in the production of DAHP by E4P, pAT1 (containing both aroG.sup.fbr and tktA) was transformed into AB2847 to eliminate the limitation of E4P. To test whether PEP supply limits DAHP production, PEP synthase (Pps) was **overexpressed** in AB2847/pAT1 by transforming plasmid pPS341 into this strain. 20-70 copies of the **pps gene** were expressed in the host cells. As a control, pPS341 was substituted by pPS341X1, which encodes an inactive, but stable **pps gene** product. The use of the inactive Pps control allowed discrimination between the effect of Pps activity and that of protein **overexpression**. AB2847/pAT1/pUHE23-2 and AB2847/pAT1 were also used without any other plasmid as additional controls to identify the effect of the cloning vector, pUHE23-2, on DAHP production.

Detailed Description Text - DETX:

As shown above, Pps **overexpression** improved DAHP production from glucose. To determine whether the basal level of pps expression in glucose medium contributed to the production of DAHP, the chromosomal **pps gene** in strain AB2847 was knocked out. The resulting strain (JCL1362) was used as the host to repeat the above experiments. Results show that inactivation of chromosomal pps did not significantly affect the DAHP production in strains containing pRW5 or pAT1 (FIG. 2B). Therefore, the basal level of pps expression in glucose medium did not contribute to the DAHP production.

Detailed Description Text - DETX:

Quinoid organics can be derived from dehydroquinate which is a down-stream metabolite of DAHP. To produce quinic acid, E. coli AB2848 aroD harboring pTW8090A which contains the gene qad (quinic acid dehydrogenase from Klebsiella pneumoniae) (ref: Draths, Ward, and Frost, 1992, JACS, 114, 9725-9726), and pKD136 (ref: same as above) which contains tkt, aroF, and aroB genes can be used as a host. The **pps gene** can be cloned into one of these plasmids and be simultaneously **overexpressed**. It has been reported that at least 80 mM of D-glucose can be converted into 25 mM of quinic acid. After cell removal, quinic acid in the supernatant can be converted into benzoquinone after addition of sulfuric acid and technical grade manganese (IV) dioxide and heating at 100.degree. C. for 1 h. In the absence of acidification, aqueous solutions of purified quinic acid are converted to hydroquinone in 10% yield upon heating at 100.degree. C. for 18 h with technical grade manganese dioxide.

Claims Text - CLTX:

(b) **overexpressing the pps and tkt genes** of said microorganisms in the glucose media; and

Claims Text - CLTX:

(b) **overexpressing the pps, tkt, and serA genes** of said microorganisms in the glucose media; and

Claims Text - CLTX:

(b) **overexpressing the pps, tkt, and pheA.sup.fbr genes** in said microorganisms in said glucose media; and

Claims Text - CLTX:

(b) **overexpressing the pps, tkt, and qad genes** in said microorganisms in the glucose media; and

US-PAT-NO: 5906925

DOCUMENT-IDENTIFIER: US 5906925 A

TITLE: Microorganisms and methods for overproduction of DAHP by cloned pps gene

DATE-ISSUED: May 25, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liao; James C.	N/A	N/A	N/A	N/A
	College Station	TX	77843-312 2	

APPL-NO: 08/ 801454

DATE FILED: February 18, 1997

PARENT-CASE:

This application is a continuation of application Ser. No. 08/307,371, filed Sep. 16, 1994, now abandoned.

US-CL-CURRENT: 435/72; 435/108 ; 435/200 ; 536/23.7 ; 536/24.1

ABSTRACT:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The **overexpression** of phosphoenol pyruvate synthase **increases** DAHP production to near theoretical yields.

28 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

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Abstract Text - ABTX:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The **overexpression** of phosphoenol pyruvate synthase **increases** DAHP production

to near theoretical yields.

Brief Summary Text - BSTX:

The present invention provides genetically engineered strains of microorganisms that **overexpress the pps gene for increasing** the production of DAHP to near theoretical yields. The present invention also provides genetically engineered strains of microorganisms where at least one of the plasmids pPS341, pPSL706, pPS706, or derivatives thereof is transformed into a microorganism for **increasing** the production of DAHP to near theoretical yields.

Brief Summary Text - BSTX:

The present invention further provides a method for **increasing** carbon flow for the biosynthesis of DAHP in a host cell comprising the steps of transforming into the host cell recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced levels relative to wild type host cells, concentrating the transformed cells through centrifugation, resuspending the cells in a minimal, nutrient lean medium, fermenting the resuspended cells, and isolating DAHP from the medium.

Brief Summary Text - BSTX:

The present invention further provides methods of **increasing** carbon flow into the common aromatic pathway of a host cell comprising the step of transforming the host cell with recombinant DNA comprising a **pps gene so that Pps** is expressed at appropriate point in the metabolic pathways at enhanced levels relative to wild type host cells.

Detailed Description Text - DETX:

The inventor have found that cell lines can be developed that **increase** the carbon flux into DAHP production and achieve near theoretical yields of DAHP by **overexpressing** phosphoenolpyruvate synthase (Pps) in the cell lines. **Overexpression** of Pps can **increase** the final concentration and yield of DAHP by as much as two-fold, to a near theoretical maximum as compared to wild type cell lines. The **overexpression** of Pps is achieved by transforming a cell line with recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced level relative to the wild type cell line and so that the yield of DAHP approaches its theoretical value.

Detailed Description Text - DETX:

Besides the use of the **pps gene,** the present invention also provides for transfer of genetic elements comprising the tkt gene, the gene coding for DAHP synthase (aroF in E. coli), the gene coding for 3-dehydroquinate synthase (aroB in E. coli), or other genes encoding enzymes that catalyze reactions in the

common aromatic pathway. Such a cell transformation can be achieved by transferring one or more plasmids that contain genes that code for enzymes that **increase** the carbon flux for DAHP synthesis and for subsequent synthesis of other desired cyclic, pre-aromatic, and aromatic metabolites. As a result of this transfer of genetic element(s), more carbon enters and moves through the common aromatic pathway relative to wild type host cells not containing the genetic elements of the present invention.

Detailed Description Text - DETX:

In one embodiment, the present invention comprises a method for **increasing** carbon flow into the common aromatic pathway of a host cell by **increasing** the production of DAHP through the **overexpression** of Pps at the appropriate point in the common aromatic pathway to provide additional PEP at the point where PEP condenses with E4P. **Increasing** carbon flow requires the step of transforming the host cell with recombinant DNA containing a **pps gene so that Pps is overexpressed** at enhanced levels relative to wild type host cells. DAHP is then produced by fermentation of the transformed cell in a nutrient medium from which the DAHP can be extracted from the medium on a batch wise or continuous extraction procedure.

Detailed Description Text - DETX:

In another embodiment, the present invention involves the co-**overexpression of a pps gene** and other genes coding for enzymes of the common aromatic pathway where additional genetic material is transformed into the host cell. The genes transferred can include the tkt gene, DAHP synthase gene and DHQ synthase gene (preferably the aroF or aroB genes, respectively). Although the work so far has centered around transforming certain host cell strains of E. coli such as AB2847 aroB, this particular host cell may not be the preferred host cell for the commercial production of DAHP or DAHP metabolites through the **overexpression** of Pps.

Detailed Description Text - DETX:

Another embodiment of the present invention is a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway. This method involves the step of **increasing** expression of Pps in the host cell relative to a wild type host cell. The step of **increasing** expression of Pps can include transferring into the host cell a vector carrying the **pps gene**. The **overexpression** of Pps results in forcing **increased** carbon flow into the biosynthesis of DAHP.

Detailed Description Text - DETX:

In another embodiment of the present invention, a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway relative to wild type host cell's biosynthetic production of such

compound is provided. This method requires the step of **increasing** expression in a host cell of a protein catalyzing conversion of pyruvate to PEP. The expression of such a protein can involve transferring into the host cell recombinant DNA including a **pps gene**.

Detailed Description Text - DETX:

One preferred embodiment of the present invention encompasses modification of a host cell to cause **overexpression** of an enzyme having the catalytic properties of naturally derived Pps, and, thereby maximizing the yield of DAHP to near theoretical yields. Enzymes having the catalytic activity of Pps include, but are not limited to, Pps produced by expression in whole cells of a naturally derived **pps gene,** enzymes produced by expression in whole cells of a naturally derived **pps gene** modified by sequence deletion or addition so that the expressed enzyme has an amino acid **sequence that varies from unmodified Pps,** abzymes produced to have catalytic sites with steric and electronic properties corresponding to catalytic sites of Pps, or other proteins produced to have the capability of catalyzing the conversion of pyruvate to PEP by any other art recognized means.

Detailed Description Text - DETX:

Additionally, the transformation of DNA, including the **pps gene,** into microorganisms engineered for the **overexpression** of other substrates, and/or **overexpression** or derepression of enzymes in the pentose phosphate or common aromatic pathway can be used to tailor the microorganism to achieve near theoretical yields of such DAHP metabolites as tyrosine, tryptophan, phenylalanine, and other aromatic metabolites such as indigo, catechol and quinoid organics such as quinic acid, benzoquinone, and hydroquinone.

Detailed Description Text - DETX:

This example demonstrates that the E. coli AB2847 is unable to utilize DAHP, and accumulates DAHP in the medium if DAHP synthase is **overexpressed**. This strain was used as a host for detecting the flux committed to the aromatic pathways. Since Draths et al. (Draths, K. M., D. L. Pompliano, D. L. Conley, J. W. Frost, A. Berry, G. L. Disbrow, R. J. Staversky, and J. C. Lievense, "Biocatalytic synthesis of aromatics from D-glucose: The role of transketolase," J. Am. Chem. Soc., 1992, 114, 3956-3962) have shown a possible limitation in the production of DAHP by E4P, pAT1 (containing both aroG.sup.fbr and tktA) was transformed into AB2847 to eliminate the limitation of E4P. To test whether PEP supply limits DAHP production, PEP synthase (Pps) was **overexpressed** in AB2847/pAT1 by transforming plasmid pPS341 into this strain. 20-70 copies of the **pps gene** were expressed in the host cells. As a control, pPS341 was substituted by pPS341X1, which encodes an inactive, but stable **pps gene** product. The use of the inactive Pps control allowed discrimination between the effect of Pps activity and that of protein **overexpression**. AB2847/pAT1/pUHE23-2 and AB2847/pAT1 were also used without any other plasmid as additional controls to identify the effect of the cloning vector, pUHE23-2,

on DAHP production.

Detailed Description Text - DETX:

As shown above, Pps **overexpression** improved DAHP production from glucose. To determine whether the basal level of pps expression in glucose medium contributed to the production of DAHP, the chromosomal **pps gene** in strain AB2847 was knocked out. The resulting strain (JCL1362) was used as the host to repeat the above experiments. Results show that inactivation of chromosomal pps did not significantly affect the DAHP production in strains containing pRW5 or pAT1 (FIG. 2B). Therefore, the basal level of pps expression in glucose medium did not contribute to the DAHP production.

Detailed Description Text - DETX:

Quinoid organics can be derived from dehydroquinate which is a down-stream metabolite of DAHP. To produce quinic acid, E. coli AB2848 aroD harboring pTW8090A which contains the gene qad (quinic acid dehydrogenase from Klebsiella pneumoniae) (ref: Draths, Ward, and Frost, 1992, JACS, 114, 9725-9726), and pKD136 (ref: same as above) which contains tkt, aroF, and aroB genes can be used as a host. The **pps gene** can be cloned into one of these plasmids and be simultaneously **overexpressed**. It has been reported that at least 80 mM of D-glucose can be converted into 25 mM of quinic acid. After cell removal, quinic acid in the supernatant can be converted into benzoquinone after addition of sulfuric acid and technical grade manganese (IV) dioxide and heating at 100.degree. C. for 1 h. In the absence of acidification, aqueous solutions of purified quinic acid are converted to hydroquinone in 10% yield upon heating at 100.degree. C. for 18 h with technical grade manganese dioxide.

Claims Text - CLTX:

(b) **overexpressing the pps and tkt genes** in said microorganisms incubated in minimal medium containing glucose; and

Claims Text - CLTX:

(b) **overexpressing the pps, tkt, and serA genes** in said microorganisms incubated in the media minimal medium containing glucose; and

Claims Text - CLTX:

(b) **overexpressing the pps, tkt, and qad genes** in said microorganisms incubated in minimal medium containing glucose; and

US-PAT-NO: 5808034

DOCUMENT-IDENTIFIER: US 5808034 A

TITLE: Plant gene construct comprising male flower specific promoters

DATE-ISSUED: September 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bridges; Ian George	Slater	IA	N/A	N/A
Bright; Simon William	Bucks	N/A	N/A	GB2
Jonathan	Maidenhead	N/A	N/A	GB2
Greenland; Andrew James	Crowthorne	N/A	N/A	GB2
Schuch; Wolfgang Walter				

APPL-NO: 08/ 293422

DATE FILED: August 22, 1994

PARENT-CASE:

This is a continuation of application Ser. No. 08/165,544, filed on Dec. 13, 1993, which was abandoned upon the filing hereof which in turn is a continuation of application Ser. No. 07/824,883, filed Jan. 22,1992, now abandoned, which is a continuation of application Ser. No. 07/470,654, filed Jan. 26, 1990, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	8901677	January 26, 1987

US-CL-CURRENT: 536/24.1; 47/DIG.1 ; 536/23.5 ; 536/23.6 ; 536/23.7

ABSTRACT:

Male sterility is imparted to a plant by a cascade of gene sequences which expresses a protein which disrupts the biosynthesis of viable pollen. Expression of the disrupter protein is restricted to male parts of the plant by an upstream promoter sequence which is specific to male flowers, the male specific promoter being under control of an operator sequence. The cascade also includes a gene encoding a repressor protein specific for that operator. Expression of the repressor protein is under control of a chemically inducible promoter which is inducible by the application to the plant by, spraying or like process, of an exogenous chemical. In the absence of the exogenous chemical inducer, no repressor protein is expressed, resulting in expression of the disrupter protein and, consequently, male sterility. Fertility may be restored to the plant, when required for maintenance of the line, by spraying with the inducer, resulting in expression of the repressor which binds the operator and inhibits expression of the disrupter protein.

8 Claims, 57 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 44

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Detailed Description Text - DETX:

Initial experiments showed that 500.mu.g/ml TPNPG was only able to retard the growth of lac.sup.+ cells, allowing the formation of small blue colonies after 48h at 28.degree. C. However, this background was eliminated in the presence of 1 mg/ml TPNPG, resulting in none of the lac.sup.+ cells plated (up to 7.times.10.sup.-7) being able to form blue colonies (Table V). In contrast, this TPNPG concentration did not noticeably affect the viability of the lac.sup.- cells. This demonstrates the high selective power of TPNPG againstlac.sup.+ cells, even when the lacY gene is chromosomal and thus at a low copy number. In this respect, the higher copy number and therefore **increased** expression level of the lac **genes on the pPS** plasmids should result in a greater waste of energy on TPNPG uptake, making the killing of lac.sup.+ cells more effective.

US-PAT-NO: 5770195

DOCUMENT-IDENTIFIER: US 5770195 A

TITLE: Monoclonal antibodies directed to the her2 receptor

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hudziak; Robert M.	Corvallis	OR	N/A	N/A
Shepard; H. Michael	Rancho Santa Fe	CA	N/A	N/A
Ullrich; Axel	Portola Valley	CA	N/A	N/A
Fendly; Brian M.	Half Moon Bay	CA	N/A	N/A

APPL-NO: 08/ 447517

DATE FILED: May 23, 1995

PARENT-CASE:

CROSS REFERENCES This application is a continuation of U.S. application Ser. No. 08/286,303 filed 5 Aug. 1994(U.S. Pat. No. 5,677,877), which application is a continuation of U.S. application Ser. No. 07/977,453 filed 18 Nov. 1992 (abandoned), which application is a continuation of U.S. application Ser. No. 07/147,461 filed 25 Jan. 1988 (abandoned), which application is a continuation-in-part of U.S. application Ser. No. 07/143,912 filed 12 Jan. 1988 (abandoned), which applications are incorporated herein by reference and to which applications priority is claimed under 35 USC .sctn.120.

US-CL-CURRENT: 424/130.1; 424/133.1 ; 424/134.1 ; 424/142.1 ; 424/143.1 ; 424/155.1 ; 424/156.1 ; 424/174.1 ; 424/183.1 ; 530/387.3 ; 530/387.7 ; 530/388.22 ; 530/388.8

ABSTRACT:

A method of inhibiting growth of tumor cells which overexpress a growth factor receptor or growth factor by treatment of the cells with antibodies which inhibit the growth factor receptor function, is disclosed. A method of treating tumor cells with antibodies which inhibit growth factor receptor function, and with cytotoxic factor(s) such as tumor necrosis factor, is also disclosed. By inhibiting growth factor receptor functions tumor cells are rendered more susceptible to cytotoxic factors.

36 Claims, 11 Drawing figures

Exemplary Claim Number: 1,14

Number of Drawing Sheets: 6

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Other Reference Publication - OREF:

Venter et al., "**Overexpression** of the c-erbB-2 Oncoprotein in Human Breast Carcinomas: Immunohistological Assessment Correlates with **Gene Amplification" Lancet pps.** 69-72 (1987).

US-PAT-NO: 5720954

DOCUMENT-IDENTIFIER: US 5720954 A

TITLE: Monoclonal antibodies directed to the HER2 receptor

DATE-ISSUED: February 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hudziak; Robert M.	Corvallis	OR	N/A	N/A
Shepard; H. Michael	Santa Fe	CA	N/A	N/A
Ullrich; Axel	Portola Valley	CA	N/A	N/A
Fendly; Brian M.	Half Moon Bay	CA	N/A	N/A

APPL-NO: 08/ 449383

DATE FILED: May 23, 1995

PARENT-CASE:

CROSS REFERENCES This application is a divisional of co-pending U.S. application Ser. No. 08/286,303 filed 5 Aug. 1994, which application is a continuation of U.S. application Ser. No. 07/977,453 filed 18 Nov. 1992 (abandoned), which application is a continuation of U.S. application Ser. No. 07/147,461 filed 25 Jan. 1988 (abandoned), which application is a continuation-in-part of U.S. application Ser. No. 07/143,912 filed 12 Jan. 1988 (abandoned), which applications are incorporated herein by reference and to which applications priority is claimed under 35 USC .intg. 120.

US-CL-CURRENT: 424/130.1; 424/138.1 ; 424/143.1 ; 424/156.1 ; 424/178.1 ; 424/198.1 ; 424/85.1 ; 530/387.7 ; 530/388.85 ; 530/391.3 ; 530/391.7

ABSTRACT:

A method of inhibiting growth of tumor cells which overexpress a growth factor receptor or growth factor by treatment of the cells with antibodies which inhibit the growth factor receptor function, is disclosed. A method of treating tumor cells with antibodies which inhibit growth factor receptor function, and with cytotoxic factor(s) such as tumor necrosis factor, is also disclosed. By inhibiting growth factor receptor functions tumor cells are rendered more susceptible to cytotoxic factors.

35 Claims, 11 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Other Reference Publication - OREF:

Venter et al., "**Overexpression** of the c-erbB-2 Oncoprotein in Human Breast Carcinomas: Immunohistological Assessment Correlates with **Gene Amplification" Lancet pps.** 69-72 (1987).

US-PAT-NO: 5072410

DOCUMENT-IDENTIFIER: US 5072410 A

TITLE: Portable "T"-configured X-Y plotter

DATE-ISSUED: December 10, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vachris; Paul F.	Palm Bay	FL	32909	N/A
Rodby; Thomas A.	Palm Bay	FL	32907	N/A

APPL-NO: 07/ 449676

DATE FILED: December 12, 1989

US-CL-CURRENT: 358/1.3; 346/139R

ABSTRACT:

A portable, X-Y plotter capable of plotting on any sized medium and work surface comprises a generally T-configured instrument transport assembly for controllably imparting a dual (X-Y) axis translation to an instrument (e.g. plotting pen) across a workpiece (paper) and controllably engaging the plotting pen with the paper during its translation. The transport assembly includes a first, generally cylindrical translation arm, which forms the top of the T-configuration and extends in a first axial direction. This first translation arm is supportable at its opposite ends on a work surface, such as a table top, upon which plotting paper is disposed. A second, generally cylindrical translation arm, which forms the vertical leg of the T, is coupled through a T-joint coupler to the first translation arm, so that the second translation arm extends in a second axial direction, orthogonal to said first axial direction. The opposite end of the second translation arm free wheels on the support surface. A plotting pen holder, which retains a plotting pen for controllable engagement with the paper, is mounted on the second translation arm for translational movement in the second direction. A dual stepper motor unit in the T-joint coupler drives a rack and pinion for the first arm and a drive belt for the pen holder. For optimal high speed operation, the stepper motors are ramped up to maximum speed, and then ramped down to avoid pen overshoot.

44 Claims, 20 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

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Detailed Description Text - DETX:

More particularly, the ideal operation of the stepper motor would be to always pulse the motor at its maximum rating. However, the sudden application of such a maximum rate pulse stream causes the motor to lock up. In order to drive the stepper motor at high pulse rates, including its maximum rating, it is necessary to gradually **increase** the rate at which the motor is pulsed. Consequently, when the control circuit of the present invention receives a high pulse rate stream, such as a **sequence of pulses at the 5000 pps** rate, rather than directly apply the high rate input to the stepper motor, it ramps up its pulse output, thereby advancing the output speed of the stepper motor in a manner that conforms with its response characteristics. On the other hand, although the motor will not tolerate the sudden application of a very high rate pulse rate input, it will follow a moderate rate pulse stream, such as one at the above-mentioned several hundred pps value. Thus, for relatively large pen excursions across the work surface, maximum effective pen speed is accomplished by ramping the motor up to maximum speed, and holding that speed over substantially the entire extent of the pen's travel path. To prevent overshoot and discontinuities at the end of the pen's excursion, the control circuitry of the present invention also ramps down the speed of the motor as it approaches the end of its advance. As a result the full capability of the stepper motor is obtained, without hindering the precision with which the pen is moved by the plotter. For limited travel distances (e.g. on the order of a half an inch), where ramping the motor would not be effective, control processor 271 bypasses the ramping mechanism and causes a direct feed of a moderate pulse rate signal to the motor.

US-PAT-NO: 4203063

DOCUMENT-IDENTIFIER: US 4203063 A

TITLE: Movement detecting apparatus and method

DATE-ISSUED: May 13, 1980

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Loeb; Paul	Glassboro	NJ	N/A	N/A
Magasiny; Irving P.	Cheltenham	NJ	N/A	N/A

APPL-NO: 05/ 828752

DATE FILED: August 29, 1977

US-CL-CURRENT: 318/603; 318/640 ; 318/653 ; 324/115 ; 324/76.48 ; 324/76.62

ABSTRACT:

Apparatus and method for detecting the movement of a control device (such as a tuning knob) for controlling the input to a controlled device (such as a frequency synthesizer or display) operating in discrete or digital steps. The rotational direction of a single tuning device such as a "tuning" knob causes an increase or decrease of the frequency. The rate of movement of the positioning device determines frequency bandswitching in differing degrees of coarse to fine tuning modes. The utilization of rotational direction and rate of the device provides a single control for all tuning functions.

The apparatus and method is useful in both open and closed (servo) loop systems.

19 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 7

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Detailed Description Text - DETX:

For the example shown in FIG. 5, when the apparatus is at an at-rest condition, the display content 170 is 0. As the tuning device 10 is rotated in a clockwise direction at the angular velocity of +V (0.6 rpm) for one second, a clock rate of C (1 pps) is generated to increment the least significant bit (LSB) up/down counter 152 by one bit to produce a count of 100 in the N Digit

display 170. This corresponds to point d.sub.1 on the contents contour. The LSB (152) is incremented because the apparatus is in slow speed control (117) mode. Further **increasing** the angular velocity +2 V (1.2 rpm) for another second causes a clock rate of 2C (2 pps) to increment the display contents by two additional LSB's obtaining a value of 300 corresponding to point d.sub.2. The LSB is incremented, it should be noted, because the slow speed mode of control 117 is still active by the continuing rotation of tuning device 10. When the angular velocity is **increased** to +3 V (1.8 rpm) for another second a clock rate of 3C (3 pps) is produced causing the speed control range to sequence from the slow (117) to medium (115) mode. In the medium speed control mode, the clock is shifted from the LSB up/down counter 152 to up/down counter 154, whereby the clock of 3 pps increments the display 170 by a count of 3,000 resulting in the sum of 3,300 as indicated by point d.sub.3. Further, **increasing** the angular velocity of tuning device 10 to +4 V (2.4 rpm) for the fourth second produces a clock rate 4C (4 **pps) causing the speed control to sequence** from medium 115 to fast 113. The clock is shifted from up/down counter 154 to up/down counter 158, whereby the clock rate of 4 pps increments the display contents 170 by a count of 400,000, to produce a total sum of 403,300 as at point d.sub.4. In this condition of fast speed control 113, **increasing** the angular velocity of tuning device 10 from +4 V (2.4 rpm) to +5 V (3.0 rpm) for the fifth second increments the display contents 170 by 500,000, to produce a sum total of 903,300 at point d.sub.5. On continuing rotating the device 10 for the sixth second, the angular velocity of movement is decreased from +5 V (3.0 rpm) to +3 V (1.8 rpm), producing a clock of 3C (3 **pps), causing the speed control to sequence** down from fast 113 to medium 115. The clock (3 pps) is shifted from up/down counter 158 to up/down counter 154 incrementing the display 170 by a count of 3,000 to produce a total sum of 906,300 as at point d.sub.6. Then as the angular velocity is further decreased to +2 V (1.2 rpm) for the seventh second, producing a clock rate of 2C (2 **pps), the speed control is sequenced** down from medium 115 to slow 117. The clock (2 pps) is accordingly shifted from up/down counter 154 to LSB up/down counter 152, to increment the display contents 170 by a count of 200, to produce a total sum of 906,500 as at point d.sub.7. At this point as the desired frequency (906,600) is being approached, the angular velocity is decreased to V (0.6 rpm) for the final, or eighth second producing a clock rate of C (1.0 pps). Slow but continuous movement of device 10 keeps the speed control in the slow (117) mode active. The clock rate (1 pps) increments the display contents 170 by a count of 100, producing the desired frequency of 906,600 as at point d.sub.8. The desired frequency tuning have been achieved, the tuning device 10 is no longer rotated whereby the angular velocity returns to 0 and the contents of the display 170 remains at the last value achieved while the device was in motion. Suitable means are provided (not shown) to hold, transfer or otherwise reset the apparatus for a new tuning operation.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	6	glnap$8	USPAT; US-PGPUB	2002/10/29 12:02
2	L2	302653	acetyl adj phosphate or acetylphosphate or acetate	USPAT; US-PGPUB	2002/10/29 12:03
3	L3	63566	promoter$1	USPAT; US-PGPUB	2002/10/29 12:03
4	L4	1256081	induc$8 or regulat$8 or activat$8 or modulat$8	USPAT; US-PGPUB	2002/10/29 12:03
5	L5	49	2 near10 4 near10 3	USPAT; US-PGPUB	2002/10/29 12:04
6	L6	7894	pps or phosphoenol adj pyruvate adj synthase1	USPAT; US-PGPUB	2002/10/29 12:06
7	L7	7896	pps or phosphoenol adj pyruvate adj synthase$1	USPAT; US-PGPUB	2002/10/29 12:06
8	L8	75	7 near4 (gene$1 or sequence$1)	USPAT; US-PGPUB	2002/10/29 12:07
9	L9	15	8 same (overexpress$ or amplif$10 or increas$8)	USPAT; US-PGPUB	2002/10/29 12:08
10	L10	13	8 and 2	USPAT; US-PGPUB	2002/10/29 12:16

[0004] Phosphoenolpyruvate (PEP) is one of the major building blocks that cells use in their biosynthetic routes, particularly in amino acid biosynthesis (see FIG. 1). For example, the synthesis of one molecule of chorismate (the common precursor to all of the aromatic amino acids) requires two molecules of PEP. To date, approaches taken to increase the influx of carbon sources into and through the common aromatic pathway typically relate to increasing the PEP supply in the cell by eliminating pyruvate kinase (pyk mutants) [1] and/or eliminating PEP carboxylase (ppc mutants) [2]. A third approach to increasing the PEP supply in the cell is to amplify the expression of the **pps gene** (encoding PEP synthase, which converts pyruvate to PEP) (U.S. Ser. No. 08/307,371, the disclosure of which is incorporated herein by reference). Additional approaches to increase the flux of carbon into and through the common aromatic pathway relate to increasing the intracellular supply of D-erythrose 4-phosphate (E4P), the other necessary precursor (with PEP) for aromatic biosynthesis. This approach may utilize overexpression of a transketolase gene (tktA or tktB), the product of which (transketolase) catalyzes the conversion of D-fructose 6-phosphate to E4P (U.S. Pat. No. 5,168,056, the disclosure of which is incorporated herein by reference). Another approach to increasing E4P availability may utilize overexpression of the transaldolase gene (talA) which encodes the enzyme transaldolase [3], which catalyzes the conversion of D-sedoheptulose 7-phosphate plus glyceraldehyde 3-phosphate to E4P plus fructose 6-phosphate.

Summary of Invention Paragraph - BSTX:

[0008] In another embodiment of the invention the host cell (which is phenotypically Pts.sup.-/glucose.sup.+) may be transformed with recombinant DNA containing genes coding for enzymes such as transketolase (tktA or tktB genes), transaldolase (talA **gene) and/or phosphoenolpyruvate synthase (pps gene**) such that the products therefrom are expressed at enhanced levels relative to wild-type host cells.

Summary of Invention Paragraph - BSTX:

[0011] In another embodiment there is provided a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway of said host cell, the method comprising the step of culturing under suitable conditions a phenotypically Pts.sup.-/glucose.sup.+ host cell. The host cell may preferably be transformed with recombinant DNA containing the tktA, tktB, talA or **pps genes** such that the products of these genes are expressed at enhanced levels relative to wild-type host cells. Alternatively, increased levels of such gene products can be achieved by chromosomal mutation or chromosomal integration by methods available to the skilled artisan. Chromosomal mutations include mutations in the tktA, tktB, talA or **pps genes** themselves, or in the promoters or regulatory genes controlling their expression. In yet another embodiment of the invention relating to the overproduction of desired compounds, the host cell may further comprise additional recombinant DNA containing one or more gene(s) coding for enzymes catalyzing reactions in the common aromatic pathway of the host cell. As for tktA, tktB, talA or **pps, increased expression of gene**(s) encoding the enzymes

of the common aromatic pathway may be effected by mutating the genes themselves, or the promoters or regulatory genes governing their expression. The host cells can be transformed with a wide variety of genes from a given pathway, depending on the desired product to be made by the cells upon fermentation.

Detail Description Paragraph - DETX:

[0107] 4) W. Holms (1986) "The central metabolic pathways of Escherichia coli: relationship between flux and control at a branch point, efficiency of conversion to biomass, and excretion of **acetate**" In: Current Topics in Cellular Regulation, Vol. 28, pp. 69-105, Academic Press, New York

PGPUB-DOCUMENT-NUMBER: 20020137204

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020137204 A1

TITLE: Techniques for growth and differentiation of human pluripotent stem cells

PUBLICATION-DATE: September 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carpenter, Melissa K.	Castro Valley	CA	US	
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Xu, Chunhui	Cupertino	CA	US	

APPL-NO: 10/ 039956

DATE FILED: October 23, 2001

RELATED-US-APPL-DATA:

child 10039956 A1 20011023 parent continuation-of 09859291 20010516 US PENDING
non-provisional-of-provisional 60175581 20000111 US
non-provisional-of-provisional 60213740 20000622 US
non-provisional-of-provisional 60213739 20000622 US
non-provisional-of-provisional 60216387 20000707 US
non-provisional-of-provisional 60220064 20000721 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
US	PCT/US01/01030	2001US-PCT/US01/01030	January 10, 2001

US-CL-CURRENT: 435/366

ABSTRACT:

This disclosure provides an improved system for culturing human pluripotent stem (pPS) cells in the absence of feeder cells. The role of the feeder cells can be replaced by supporting the culture on an extracellular matrix, and culturing the cells in a conditioned medium. Permanent cell lines are provided that can produce conditioned medium on a commercial scale. Methods have also been discovered to genetically alter pPS cells by introducing the cells with a viral vector or DNA/lipid complex. The system described in this disclosure allows for bulk proliferation of pPS cells for use in studying the biology of pPS cell differentiation, and the production of important products for use in human therapy.

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Ser. No. 09/859,291, filed May 16, 2001, and claims priority to the following patent applications: U.S. Ser. No. 60/175,581, filed Jan. 11, 2000; U.S. Ser. No. 60/213,740, filed Jun. 22, 2000; U.S. Ser No. 60/213,739, filed Jun. 22, 2000; U.S. Ser. No. 60/216,387, filed Jul. 7, 2000; U.S. Ser. No. 60/220,064, filed Jul. 21, 2000; U.S. Ser. No. 09/688,031, filed Oct. 10, 2000; and PCT/US01/01030, (designating the U.S.) filed Jan. 10, 2001, and published as WO 01/51616 on Jul. 19, 2001.

[0002] The priority applications are hereby incorporated herein by reference in their entirety.

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Summary of Invention Paragraph - BSTX:

[0022] This disclosure also provides a method of producing an mRNA preparation or a cDNA library from primate pluripotent stem (pPS) cells before or after differentiation, comprising providing a culture of undifferentiated pPS cells essentially free of feeder cells, optionally permitting the pPS cells to differentiate, and isolating mRNA from the undifferentiated or differentiated cells. These techniques can be used to prepare cDNA expression and subtraction libraries. When the mRNA is obtained from feeder-free pPS cultures, the cDNA libraries may comprise at least 1,000 genes expressed at the mRNA level in either undifferentiated pPS cells, or cells differentiated from pPS cells, and be essentially free of cDNA of other vertebrates. Sequence information for **genes expressed in undifferentiated pPS** cells, and their differentiated progeny, can be used to prepare cDNA and protein derivatives of the expressed genes, and specific antibody to the gene product.

Detail Description Paragraph - DETX:

[0098] As illustrated in the examples below, medium that has been conditioned for 1-2 days is typically used to support pPS cell culture for 1-2 days, and then exchanged. The medium can be used directly after conditioning, it can be stored neat or as an extract (e.g., for 2, 6, or 14 days at 4.degree. C., or frozen at -20.degree. C.). Caution should be taken in filtering the medium: some filters such as cellulose **acetate** 20 .mu. non-protein binding membranes (Corning # 430769) can be suitable where others remove activity. In initial studies, medium is typically used undiluted. Efficacy of dilutions and other manipulations can be assessed by maintaining pPS cells with the medium for 7 days or longer, and determining whether the cultures maintain features characteristic of undifferentiated pPS cells.

Detail Description Paragraph - DETX:

[0164] Of particular interest are libraries optimized for expression of the

cDNA in pluripotent stem cells. Methylation patterns and other regulatory control mechanisms in embryonic cells can suppress transcription of genes under control of promoters such as CMV, which are active in most other eukaryotic cell types. It has been discovered that promoters for house-keeping **genes active in pPS** cells may be effective for controlling transcription of artificially introduced encoding regions. As illustrated in Example 14, an appropriate promoter can be selected experimentally using reporter constructs comprising test promoter sequences, a reporter gene such as green fluorescent protein or .beta.-galactosidase, and a drug resistance gene. An appropriate promoter will have the characteristic of causing expression of the reporter gene, without substantially increasing the proportion of cells lost to differentiation. Using this selection strategy, the promoter for PGK, EF1.alpha., and UbiC have been determined as effective for construction of libraries expressible in pPS cells.

Detail Description Paragraph - DETX:

[0167] Libraries that represent less complex mRNA sources have relatively fewer independent gene sequences represented in a given number of cDNAs compared to libraries made from more complex mRNA sources. In certain embodiments of this invention, mRNA preparations, cDNA preparations, and libraries in cloning vectors contain sequences representing at least 100, 1,000, 10,000, or even 50,000 **genes expressed at the mRNA level in pPS** cells or their differentiated progeny.

Detail Description Paragraph - DETX:

[0171] Once the **sequence of an mRNA or cDNA from pPS** cells or their differentiated progeny has been determined, it can be used in the manufacture of polynucleotides that contain such sequences, polypeptides they encode, and antibody specific for the polypeptides.

Detail Description Paragraph - DETX:

[0175] The **sequence data of an mRNA or cDNA from pPS** cells can also be used to manufacture peptides that comprise a sequence contained in an encoding region. Amino acid sequences can be modified to remove or add segments, or introduce mutations and other changes for any desirable purpose. Substantially identical polypeptides or polypeptide fragments share an epitope recognized by an antibody specific for a protein encoded in a cDNA of an expression library from pPS cells or their differentiated progeny, in preference to other nucleotide sequences contained in the human genome or expressed in other cell types. In certain embodiments, the peptides are 60%, 80%, 90%, 95%, or 100% identical to a peptide or peptide fragment encoded in the mRNA or cDNA, in order of increasing preference. The length of the identical or homologous sequence compared with the prototype polypeptide can be about 7,10, 15, 25, 50 or 100 residues in order of increasing preference, up to the length of the entire protein.

Detail Description Paragraph - DETX:

[0179] Polynucleotides, polypeptides, and antibody derived from sequence data obtained from mRNA or cDNA of this invention have a number of important commercial applications. For example, **genes or proteins that are expressed in pPS** cells but decrease during differentiation can be used as molecular markers of the undifferentiated state. Reagents corresponding to these markers, such as antibodies, can be used to eliminate undifferentiated pPS cells from a population of differentiated cells by immunoaffinity isolation or complement-mediated lysis. Genes or proteins that increase expression levels during differentiation can be used in a similar manner to purify, enrich, remove or eliminate specific cell types derived from pPS cells. These markers may serve as indicators of broad classes of cell differentiation, such as genes or proteins expressed in mesodermal, endodermal or ectodermal lineages, or may serve as specific markers of a confined spectrum of highly differentiated cell types.

PGPUB-DOCUMENT-NUMBER: 20020127678

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020127678 A1

TITLE: Process for the fermentative preparation of L-threonine

PUBLICATION-DATE: September 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Rieping, Mechthild	Bielefeld		DE	
Thierbach, Georg	Bielefeld		DE	
Van Der Rest, Michel	Venlo		NL	
Eduard	Baesweler		DE	
Molenaar, Douwe				

APPL-NO: 09/ 801042

DATE FILED: March 8, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60229329 20000901 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	100 34 833.5	2000DE-100 34 833.5	July 18, 2000
DE	101 03 874.7	2001DE-101 03 874.7	January 30, 2001

US-CL-CURRENT: 435/189,435/252.3 ,435/320.1 ,435/69.1 ,536/23.2

ABSTRACT:

The invention provides a process for the fermentative preparation of L-threonine using Enterobacteriaceae which in particular already produce L-threonine and in which the nucleotide sequence(s) which code(s) for the mqo gene are enhanced, in particular over-expressed.

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Summary of Invention Paragraph - BSTX:

[0067] the **pps gene which codes for phosphoenol pyruvate synthase** (Molecular and General Genetics 231:332 (1992)),

Detail Description Paragraph - DETX:

[0132] Five times, 200 ml LB medium were treated with 100 .mu.g/ml carbenicillin and 100 .mu.M isopropyl .beta.-D-thiogalactoside (IPTG), inoculated with in each case a colony of the strain MC4100.DELTA.mqo/pUCH2 and in each case cultured in 1 l conical flasks for 16 hours at 37.degree. C. and 200 revolutions per minute. The cells were washed twice in buffer A (50 mM hepes, 10 mM potassium **acetate,** 10 mM CaCl.sub.2, 5 mM MgCl.sub.2, adjusted to pH 7.5 with NaOH) at 4.degree. C. and resuspended in 40 ml of the same buffer. The cells were then broken down twice in a precooled French Pressure Cell from Spectronic Unicam (Rochester, N.Y., USA) under 69 MPa (mega-Pascal). The cell debris was then sedimented twice in a centrifuge at 4.degree. C. for 10 minutes at 10000.times.g. The supernatant was then centrifuged for 30 minutes at 75000.times.g and 4.degree. C. The membrane pellet was resuspended with the same volume of buffer B (50 mM Na phosphate, 200 mM NaCl, pH 7.5) and centrifuged again for 30 minutes at 75000.times.g and 4.degree. C. The pellet was then resuspended with 1 ml buffer B. The histidine-tagged malate:quinone oxidoreductase protein was purified in two steps.

Claims Text - CLTX:

11. A process as claimed in claim 5, wherein the **pps gene which codes for phosphoenol pyruvate synthase** is enhanced at the same time.

PGPUB-DOCUMENT-NUMBER: 20020091244

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020091244 A1

TITLE: Human signal peptide-containing proteins

PUBLICATION-DATE: July 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
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Hillman, Jennifer L.	Mountain View	CA	US	
Corley, Neil C.	Mountain View	CA	US	
Guegler, Karl J.	Menlo Park	CA	US	
Baughn, Mariah R.	San Jose	CA	US	
Sather, Susan K.	Palo Alto	CA	US	
Shah, Purvi	Sunnyvale	CA	US	

APPL-NO: 09/ 799777

DATE FILED: March 5, 2001

RELATED-US-APPL-DATA:

child 09799777 A1 20010305 parent division-of 09002485 19971231 US PENDING

US-CL-CURRENT: 536/23.1,530/350

ABSTRACT:

The invention provides a human signal peptide-containing proteins, the polynucleotides which encode them and methods for their use. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention further provides methods for diagnosing or treating disorders associated with expression of the proteins

[0001] This application is a divisional of U.S. Ser. No. 09/002,485 filed on Dec. 31, 1997.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX:

[0011] Protein phosphatases remove phosphate groups from molecules previously modified by protein kinases thus participating in cell signaling, proliferation, differentiation, contacts, and oncogenesis. Protein

phosphorylation is a key strategy used to control protein functional activity in eukaryotic cells. The high energy phosphate is transferred from ATP to a protein by protein kinases and removed by protein phosphatases. There appear to be three, evolutionarily-distinct protein phosphatase **gene families: protein phosphatases (PPs)**; protein tyrosine phosphatases (PTPs); and acid/alkaline phosphatases (APs). PPs dephosphorylate phosphoserine/threonine residues and are an important regulator of many cAMP mediated, hormone responses in cells. PTPs reverse the effects of protein tyrosine kinases and therefore play a significant role in cell cycle and cell signaling processes. Although APs dephosphorylate substrates in vitro, their role in vivo is not well known (Carbonneau and Tonks (1992) Annu Rev Cell Biol 8:463-493).

Detail Description Paragraph - DETX:

[0361] The frozen tissue was homogenized and lysed using a POLYTRON homogenizer (Brinkmann Instruments, Westbury N.J.) in guanidinium isothiocyanate solution. The lysate was centrifuged over a 5.7 M CsCl cushion using an SW28 rotor in an L8-70M ultracentrifuge (Beckman Coulter, Fullerton Calif.) for 18 hours at 25,000 rpm at ambient temperature. The RNA was extracted with acid phenol, pH 4.0, precipitated using 0.3 M sodium **acetate** and 2.5 volumes of ethanol, resuspended in RNAse-free water and DNase treated at 37.degree. C. The RNA extraction and precipitation were repeated as before. The mRNA was then isolated using the OLIGOTEX kit (Qiagen, Chatsworth Calif.) and used to construct the cDNA library.

PGPUB-DOCUMENT-NUMBER: 20020090723

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020090723 A1

TITLE: Techniques for growth and differentiation of human pluripotent stem cells

PUBLICATION-DATE: July 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carpenter, Melissa K.	Castro Valley	CA	US	
Inokuma, Margaret S.	San Jose	CA	US	
Xu, Chunhui	Cupertino	CA	US	

APPL-NO: 09/ 994440

DATE FILED: November 26, 2001

RELATED-US-APPL-DATA:

child 09994440 A1 20011126 parent continuation-of 09859291 20010516 US PENDING
non-provisional-of-provisional 60175581 20000111 US
non-provisional-of-provisional 60213740 20000622 US
non-provisional-of-provisional 60213739 20000622 US
non-provisional-of-provisional 60216387 20000707 US
non-provisional-of-provisional 60220064 20000721 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
US	PCT/US01/01030	2001US-PCT/US01/01030	January 10, 2001
WO	01/51616	2001WO-01/51616	July 19, 2001

US-CL-CURRENT: 435/366,435/368

ABSTRACT:

This disclosure provides an improved system for culturing human pluripotent stem (pPS) cells in the absence of feeder cells. The role of the feeder cells can be replaced by supporting the culture on an extracellular matrix, and culturing the cells in a conditioned medium. Permanent cell lines are provided that can produce conditioned medium on a commercial scale. Methods have also been discovered to genetically alter pPS cells by introducing the cells with a viral vector or DNA/lipid complex. The system described in this disclosure allows for bulk proliferation of pPS cells for use in studying the biology of pPS cell differentiation, and the production of important products for use in human therapy.

REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Ser. No. 09/859,291, filed May 16, 2001, and claims priority to the following patent applications: U.S. Ser. No. 60/175,581, filed Jan. 11, 2000; U.S. Ser. No. 60/213,740, filed Jun. 22, 2000; U.S. Ser. No. 60/213,739, filed Jun. 22, 2000; U.S. Ser. No. 60/216,387, filed Jul. 7, 2000; U.S. Ser. No. 60/220,064, filed Jul.21, 2000; U.S. Ser. No. 09/688,031, filed Oct. 10, 2000; and PCT/US01/01030, (designating the U.S.) filed Jan. 10, 2001, and published as WO 01/51616 on Jul. 19, 2001.
[0002] The priority applications are hereby incorporated herein by reference in their entirety.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX:

[0022] This disclosure also provides a method of producing an mRNA preparation or a cDNA library from primate pluripotent stem (pPS) cells before or after differentiation, comprising providing a culture of undifferentiated pPS cells essentially free of feeder cells, optionally permitting the pPS cells to differentiate, and isolating mRNA from the undifferentiated or differentiated cells. These techniques can be used to prepare cDNA expression and subtraction libraries. When the mRNA is obtained from feeder-free pPS cultures, the cDNA libraries may comprise at least 1,000 genes expressed at the mRNA level in either undifferentiated pPS cells, or cells differentiated from pPS cells, and be essentially free of cDNA of other vertebrates. Sequence information for **genes expressed in undifferentiated pPS** cells, and their differentiated progeny, can be used to prepare cDNA and protein derivatives of the expressed genes, and specific antibody to the gene product.

Detail Description Paragraph - DETX:

[0105] As illustrated in the examples below, medium that has been conditioned for 1-2 days is typically used to support pPS cell culture for 1-2 days, and then exchanged. The medium can be used directly after conditioning, it can be stored neat or as an extract (e.g., for 2, 6, or 14 days at 40C, or frozen at -20.degree. C.). Caution should be taken in filtering the medium: some filters such as cellulose **acetate** 20 p non-protein binding membranes (Corning # 430769) can be suitable where others remove activity. In initial studies, medium is typically used undiluted. Efficacy of dilutions and other manipulations can be assessed by maintaining pPS cells with the medium for 7 days or longer, and determining whether the cultures maintain features characteristic of undifferentiated pPS cells.

Detail Description Paragraph - DETX:

[0181] Of particular interest are libraries optimized for expression of the cDNA in pluripotent stem cells. Methylation patterns and other regulatory

control mechanisms in embryonic cells can suppress transcription of genes under control of promoters such as CMV, which are active in most other eukaryotic cell types. It has been discovered that promoters for house-keeping **genes active in pPS** cells may be effective for controlling transcription of artificially introduced encoding regions. As illustrated in Example 14, an appropriate promoter can be selected experimentally using reporter constructs comprising test promoter sequences, a reporter gene such as green fluorescent protein or .beta.-galactosidase, and a drug resistance gene. An appropriate promoter will have the characteristic of causing expression of the reporter gene, without substantially increasing the proportion of cells lost to differentiation. Using this selection strategy, the promoter for PGK, EF1.alpha., and UbiC have been determined as effective for construction of libraries expressible in pPS cells.

Detail Description Paragraph - DETX:

[0185] Libraries that represent less complex mRNA sources have relatively fewer independent gene sequences represented in a given number of cDNAs compared to libraries made from more complex mRNA sources. In certain embodiments of this invention, mRNA preparations, cDNA preparations, and libraries in cloning vectors contain sequences representing at least 100, 1,000, 10,000, or even 50,000 **genes expressed at the mRNA level in pPS** cells or their differentiated progeny.

Detail Description Paragraph - DETX:

[0190] Once the **sequence of an mRNA or cDNA from pPS** cells or their differentiated progeny has been determined, it can be used in the manufacture of polynucleotides that contain such sequences, polypeptides they encode, and antibody specific for the polypeptides.

Detail Description Paragraph - DETX:

[0194] The **sequence data of an mRNA or cDNA from pPS** cells can also be used to manufacture peptides that comprise a sequence contained in an encoding region. Amino acid sequences can be modified to remove or add segments, or introduce mutations and other changes for any desirable purpose. Substantially identical polypeptides or polypeptide fragments share an epitope recognized by an antibody specific for a protein encoded in a cDNA of an expression library from pPS cells or their differentiated progeny, in preference to other nucleotide sequences contained in the human genome or expressed in other cell types. In certain embodiments, the peptides are 60%, 80%, 90%, 95%, or 100% identical to a peptide or peptide fragment encoded in the mRNA or cDNA, in order of increasing preference. The length of the identical or homologous sequence compared with the prototype polypeptide can be about 7, 10, 15, 25, 50 or 100 residues in order of increasing preference, up to the length of the entire protein.

Detail Description Paragraph - DETX:

[0198] Polynucleotides, polypeptides, and antibody derived from sequence data obtained from mRNA or cDNA of this invention have a number of important commercial applications. For example, **genes or proteins that are expressed in pPS** cells but decrease during differentiation can be used as molecular markers of the undifferentiated state. Reagents corresponding to these markers, such as antibodies, can be used to eliminate undifferentiated pPS cells from a population of differentiated cells by immunoaffinity isolation or complement-mediated lysis. Genes or proteins that increase expression levels during differentiation can be used in a similar manner to purify, enrich, remove or eliminate specific cell types derived from pPS cells. These markers may serve as indicators of broad classes of cell differentiation, such as genes or proteins expressed in mesodermal, endodermal or ectodermal lineages, or may serve as specific markers of a confined spectrum of highly differentiated cell types.

PGPUB-DOCUMENT-NUMBER: 20020081724

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020081724 A1

TITLE: Techniques for growth and differentiation of human pluripotent stem cells

PUBLICATION-DATE: June 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Carpenter, Melissa K.	Castro Valley	CA	US	
Funk, Walter D.	Hayward	CA	US	
Gold, Joseph D.	San Francisco	CA	US	
Inokuma, Margaret S.	San Jose	CA	US	
Xu, Chunhui	Cupertino	CA	US	

APPL-NO: 09/ 859291

DATE FILED: May 16, 2001

RELATED-US-APPL-DATA:

child 09859291 A1 20010516 parent continuation-of PCT/US01/01030 20010110 US
UNKNOWN non-provisional-of-provisional 60175581 20000111 US
non-provisional-of-provisional 60213740 20000622 US
non-provisional-of-provisional 60213739 20000622 US
non-provisional-of-provisional 60216387 20000707 US
non-provisional-of-provisional 60220064 20000721 US

US-CL-CURRENT: 435/366,435/354 ,435/384

ABSTRACT:

This disclosure provides an improved system for culturing human pluripotent stem (pPS) cells in the absence of feeder cells. The role of the feeder cells can be replaced by supporting the culture on an extracellular matrix, and culturing the cells in a conditioned medium. Permanent cell lines are provided that can produce conditioned medium on a commercial scale. Methods have also been discovered to genetically alter pPS cells by introducing the cells with a viral vector or DNA/lipid complex. The system described in this disclosure allows for bulk proliferation of pPS cells for use in studying the biology of pPS cell differentiation, and the production of important products for use in human therapy.

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to the following pending U.S. patent

applications: U.S. Ser. No. 60/175,581, filed Jan. 11, 2000; U.S. Ser. No. 60/213,740, filed Jun. 22, 2000; U.S. Ser. No. 60/213,739, filed Jun. 22, 2000; U.S. Ser. No. 60/216,387, filed Jul. 7, 2000; U.S. Ser. No. 60/220,064, filed Jul. 21, 2000; and U.S. Ser. No. 09/688,031, filed Oct. 10, 2000.

[0002] For purposes of prosecution in the U.S., the priority applications are hereby incorporated herein by reference in their entirety.

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Summary of Invention Paragraph - BSTX:

[0022] This disclosure also provides a method of producing an mRNA preparation or a cDNA library from primate pluripotent stem (pPS) cells before or after differentiation, comprising providing a culture of undifferentiated pPS cells essentially free of feeder cells, optionally permitting the pPS cells to differentiate, and isolating mRNA from the undifferentiated or differentiated cells. These techniques can be used to prepare cDNA expression and subtraction libraries. When the mRNA is obtained from feeder-free pPS cultures, the cDNA libraries may comprise at least 1,000 genes expressed at the mRNA level in either undifferentiated pPS cells, or cells differentiated from pPS cells, and be essentially free of cDNA of other vertebrates. Sequence information for **genes expressed in undifferentiated pPS** cells, and their differentiated progeny, can be used to prepare cDNA and protein derivatives of the expressed genes, and specific antibody to the gene product.

Detail Description Paragraph - DETX:

[0102] As illustrated in the examples below, medium that has been conditioned for 1-2 days is typically used to support pPS cell culture for 1-2 days, and then exchanged. The medium can be used directly after conditioning, it can be stored neat or as an extract (e.g., for 2, 6, or 14 days at 4.degree. C., or frozen at -20.degree. C.). Caution should be taken in filtering the medium: some filters such as cellulose **acetate** 20.mu. non-protein binding membranes (Corning #430769) can be suitable where others remove activity. In initial studies, medium is typically used undiluted. Efficacy of dilutions and other manipulations can be assessed by maintaining pPS cells with the medium for 7 days or longer, and determining whether the cultures maintain features characteristic of undifferentiated pPS cells.

Detail Description Paragraph - DETX:

[0178] Of particular interest are libraries optimized for expression of the cDNA in pluripotent stem cells. Methylation patterns and other regulatory control mechanisms in embryonic cells can suppress transcription of genes under control of promoters such as CMV, which are active in most other eukaryotic cell types. It has been discovered that promoters for house-keeping **genes active in pPS** cells may be effective for controlling transcription of artificially introduced encoding regions. As illustrated in Example 14, an

appropriate promoter can be selected experimentally using reporter constructs comprising test promoter sequences, a reporter gene such as green fluorescent protein or .beta.-galactosidase, and a drug resistance gene. An appropriate promoter will have the characteristic of causing expression of the reporter gene, without substantially increasing the proportion of cells lost to differentiation. Using this selection strategy, the promoter for PGK, EF1.alpha., and UbiC have been determined as effective for construction of libraries expressible in pPS cells.

Detail Description Paragraph - DETX:

[0182] Libraries that represent less complex mRNA sources have relatively fewer independent gene sequences represented in a given number of cDNAs compared to libraries made from more complex mRNA sources. In certain embodiments of this invention, mRNA preparations, cDNA preparations, and libraries in cloning vectors contain sequences representing at least 100, 1,000, 10,000, or even 50,000 **genes expressed at the mRNA level in pPS** cells or their differentiated progeny.

Detail Description Paragraph - DETX:

[0187] Once the **sequence of an mRNA or cDNA from pPS** cells or their differentiated progeny has been determined, it can be used in the manufacture of polynucleotides that contain such sequences, polypeptides they encode, and antibody specific for the polypeptides.

Detail Description Paragraph - DETX:

[0191] The **sequence data of an mRNA or cDNA from pPS** cells can also be used to manufacture peptides that comprise a sequence contained in an encoding region. Amino acid sequences can be modified to remove or add segments, or introduce mutations and other changes for any desirable purpose. Substantially identical polypeptides or polypeptide fragments share an epitope recognized by an antibody specific for a protein encoded in a cDNA of an expression library from pPS cells or their differentiated progeny, in preference to other nucleotide sequences contained in the human genome or expressed in other cell types. In certain embodiments, the peptides are 60%, 80%, 90%, 95%, or 100% identical to a peptide or peptide fragment encoded in the mRNA or cDNA, in order of increasing preference. The length of the identical or homologous sequence compared with the prototype polypeptide can be about 7, 10, 15, 25, 50 or 100 residues in order of increasing preference, up to the length of the entire protein.

Detail Description Paragraph - DETX:

[0195] Polynucleotides, polypeptides, and antibody derived from sequence data obtained from mRNA or cDNA of this invention have a number of important commercial applications. For example, **genes or proteins that are expressed in pPS** cells but decrease during differentiation can be used as molecular markers

of the undifferentiated state. Reagents corresponding to these markers, such as antibodies, can be used to eliminate undifferentiated pPS cells from a population of differentiated cells by immunoaffinity isolation or complement-mediated lysis. Genes or proteins that increase expression levels during differentiation can be used in a similar manner to purify, enrich, remove or eliminate specific cell types derived from pPS cells. These markers may serve as indicators of broad classes of cell differentiation, such as genes or proteins expressed in mesodermal, endodermal or ectodermal lineages, or may serve as specific markers of a confined spectrum of highly differentiated cell types.

US-PAT-NO: 6472169

DOCUMENT-IDENTIFIER: US 6472169 B1

TITLE: Biocatalytic synthesis of shikimic acid

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Frost; John W.	Okemos	MI	N/A	N/A
Frost; Karen M.	Okemos	MI	N/A	N/A
Knop; David R.	Okemos	MI	N/A	N/A

APPL-NO: 09/ 676609

DATE FILED: September 30, 2000

PARENT-CASE:

This application is a continuation-in-part of Ser. No. 09/240,440 filed Jan. 29, 1999.

US-CL-CURRENT: 435/41; 435/127 ; 435/156 ; 435/189 ; 435/193 ; 435/232 ; 435/252.3 ; 435/320.1 ; 435/822 ; 435/849 ; 435/911 ; 435/940 ; 536/23.2

ABSTRACT:

A bioengineered synthesis scheme for the production of shikimic acid from a carbon source is provided. Methods of producing shikimic acid from a carbon source based on the synthesis scheme are also provided.

21 Claims, 13 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

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Detailed Description Text - DETX:

In a further embodiment, the E. coli comprises plasmid pKD15.071B. This plasmid is derived from and carries the same **gene inserts as pKD12.138 as well as a pps gene** insert encoding for phosphoenolpyruvate (PEP) synthase. PEP synthase catalyzes the conversion of pyruvate back to PEP. Elevated expression of PEP synthase along with transketolase provides an increase in the amount of shikimic acid produced.

Detailed Description Text - DETX:

In an alternate preferred embodiment, the recombinant E. coli comprises plasmid pSC6.162A. This plasmid is derived from and carries the same **gene inserts as pKD12.138 as well as pps P.sub.tac glf gene** insert encoding for glucose facilitator protein and PEP synthase.

Detailed Description Text - DETX:

In another embodiment, the aroF.sup.FBR, serA, aroE, tkt, **pps, glf and/or glk genes** are inserted directly into the genome of the host cell. Thus a plasmid would not be required for the production of shikimic acid from such a recombinant microbe.

Detailed Description Text - DETX:

Plasmid pKD15.071B (11.9 kb) was constructed by replacing the 1.0-kb .beta.-lac **gene of pKD12.138A by the pps** fragment from pKL1.87B. Plasmid pKL1.87B was digested with BamHI and HindIII and the resulting 3.0-kb pps fragment was treated with Klenow fragment. Following digestion of pKD12.138A with NcoI, the 8.9-kb fragment was modified to blunt ends using Klenow fragment. Ligation of these two purified fragments yielded pKD15.071A. The **pps gene** is transcribed in the opposite orientation relative to the tktA gene.

Detailed Description Text - DETX:

Plasmid pSC 6.142B (7.5 kb) was created by inserting the glf gene into pKL1.87A. Plasmid pTC325 was digested with BamHI, HindIII and XbaI and the resulting 2.2-kb P.sub.tac glf fragment was treated with Klenow fragment. Plasmid pKL1.87A was linearized by digestion with SalI followed by treatment with Klenow fragment. Ligation of the P.sub.tac glf fragment into pKL1.87A afforded pSC6.142B. The P.sub.tac glf gene is transcribed in the opposite orientation relative to the **pps gene**.

Detailed Description Text - DETX:

Plasmid pSC6.162A (14.1 kb) was constructed by inserting the 5.2-kb PpsP.sub.tac glf cassette from pSC6.142B into pKD12.138. Plasmid pSC6.142B was digested with BamHI and HindIII followed by treatment of the ppsP.sub.ta glf fragment with Klenow fragment. The 1.0-kb .beta.-lac gene was excised from the 9.9-kb plasmid pKD12.138A and the remaining 8.9-kb fragment was treated with Klenow fragment. Ligation of the two purified DNA fragments afforded pSC6.162A. The P.sub.tac glf fragment was transcribed in the same orientation and the **pps gene** in the opposite orientation relative to the tktA gene.

Detailed Description Text - DETX:

With conditions established that adequately suppress quinic acid formation without significantly compromising control, attention was turned to increasing shikimic acid titers using transketolase overexpression. When cultured in the presence of 1 mM M.sub..alpha. DG, SP1.1/pKD12.138 synthesized 51.1 g/L of shikimic acid and 4.3 g/L of quinic acid, affording a molar ratio exceeding 13 (Table 3). Transketolase expression resulted in a 25% increase in shikimic acid titers while maintaining a molar ratio of shikimic acid to quinic acid that allows shikimic acid isolation. The concentration of DHS byproduct also increased to 8.8 g/L, providing added incentive to obtain a shikimate dehydrogenase insensitive to shikimic acid inhibition. When SP2.1/pKD12.138 was cultured under standard conditions, the fermentation never reached the point of phase change. At 33.degree. C. growth of SP2.1/pKD12.138 was slow and resulted in significant **acetate** production.

Detailed Description Text - DETX:

Following treatment of the solution with carbon, the dark color was less intense than prior to treatment, but the solution was not colorless. Addition of glacial acetic acid to a final concentration of 15% afforded a clear, yellow solution which was then eluted through a column of AG1-x8 (**acetate** form, 5 cm.times.20 cm) at 4.degree. C. Following elution of the column with an additional 400 mL of 15% aqueous acetic acid, the combined eluents were passed through a column of Dowex 50 (H.sup.+ form, 5 cm.times.20 cm) at 4.degree. C. which was then washed with 400 mL of 15% aqueous acetic acid. The eluents off the cation exchange column were combined and concentrated to approximately 150 mL by boiling and then to dryness by rotary evaporation, leaving a hard white solid (83% recovery through this step). Recrystallization from a mixture of methanol and ethyl **acetate** afforded shikimic acid as a fine white powder (61% recovery based on shikimic acid quantified in crude fermentation broth).

US-PAT-NO: 6344600

DOCUMENT-IDENTIFIER: US 6344600 B1

TITLE: Method for producing human hemoglobin proteins using plant cells

DATE-ISSUED: February 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Merot; Bertrand	Volvic	N/A	N/A	FR
Dieryck; Wilfrid	Saint-Pathus	N/A	N/A	FR
Lenee; Philippe	Noumea	N/A	N/A	FR
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Gruber; Veronique	Chamalieres	N/A	N/A	FR
Pagnier; Renee-Josee	Le Paris	N/A	N/A	FR
Baudino; Sylvie	Kremlin-Bicetre	N/A	N/A	FR
Poyart; Claude	Orcines	N/A	N/A	FR

APPL-NO: 08/ 983564

DATE FILED: June 9, 1998

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	95 08615	July 17, 1995

PCT-DATA:
APPL-NO: PCT/FR96/01123
DATE-FILED: July 17, 1996
PUB-NO: WO97/04115
PUB-DATE: Feb 6, 1997
371-DATE: Jun 9, 1998
102(E)-DATE: Jun 9, 1998

US-CL-CURRENT: 800/288; 435/410 ; 435/419 ; 435/430 ; 435/468 ; 536/23.1 ; 536/23.5 ; 800/278 ; 800/298

ABSTRACT:

A method for producing human hemoglobin proteins by (i) inserting into plant cells one or more nucleic acid molecules that each comprise at least one sequence coding for a protein component of a human hemoglobin protein capable of reversibly binding oxygen, and optionally a sequence coding for a selection agent; (ii) selecting cells containing nucleic acid coding for the protein component of the human hemoglobin protein; (iii) optionally propagating the transformed cells either in a culture or by regenerating whole transgenic or chimeric plants; and (iv) recovering and optionally purifying the human hemoglobin protein that includes a complex consisting of the protein or

proteins coded for by the nucleic acid and at least one iron-containing polphyritic nucleus, or a plurality of such complexes.

23 Claims, 11 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 11

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Detailed Description Text - DETX:

The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml tetracycline, was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with restriction enzymes. Next, the HindIII restriction site of the plasmid DNA of the selected clone was modified at an EcoRI restriction site with the aid of a phosphorylated HindIII--EcoRI adaptor (Stratagene Cloning Systems). To carry out this modification, 500 ng of plasmid DNA of the selected clone were digested with HindIII, dephosphorylated with the enzyme calf intestinal alkaline phosphatase (Boehringer Mannheim) according to the manufacturer's recommendations and coprecipitated in the presence of 1500 ng of HindIII-EcoRI adaptor DNA, 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min. After centrifugation at 12000 g for 30 min. the precipitated DNA was washed with 70% ethanol, dried, taken up in 8 .mu.l of water, heated at 65.degree. C. for 10 min, and then ligated in the presence of 1 .mu.l of 10.times.T4 DNA ligase buffer (Amersham) and 2.5 U of the enzyme T4 DNA ligase (Amersham) at 14.degree. C. for 16 hours. After inactivation of the T4 DNA ligase at 65.degree. C. for 10 min, the ligation reaction mixture was digested with EcoRI, purified by electrophoresis on a 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol and then dried. The E. coli DH5.alpha. bacteria previously made competent were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml tetracyclin, was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with HindIII and EcoRI in particular. The resulting binary plasmid, which now possesses only the last 9 codons of the coding sequences of the cat gene and in which the EcoRI site is unique, was called pBIOC4.

Detailed Description Text - DETX:

The expression cassette, consisting of the pd35S promoter and the 35S polyA terminator, was isolated from the plasmid pJIT163D. The plasmid pJIT163D is derived from the plasmid pJIT163 which is itself derived from the plasmid pJIT60 (Guerineau and Mullineaux, 1993). The plasmid pJIT163 possesses an ATG codon between the HindIII and SalI sites of the polylinker. To eliminate this ATG and to obtain the plasmid pJIT163D, the plasmid DNA pJIT163 was doubly

digested with HindIII and SalI, purified by electrophoresis on a 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol, dried, subjected to the action of the Klenow enzyme (New England Biolabs) according to the manufacturer's recommendations, deproteinized by extraction with 1 volume of phenol:chloroform:isoamyl alcohol (25:24:1) and then 1 volume of chloroform:isoamyl alcohol (24:1), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol, dried and finally ligated in the presence of 1 .mu.l of 10.times.T4 DNA ligase buffer (Amersham) and 2.5 U of T4 DNA ligase enzyme (Amersham) at 14.degree. C. for 16 hours. The E. coli DH5.alpha. bacteria previously made competent, were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 50 .mu.g/ml ampicillin, was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with restriction enzymes. To isolate the expression cassette consisting of the pd35S promoter and of the 35S polyA terminator (SacI-XhoI fragment), the plasmid DNA of the pJIT163D clone selected was digested with SacI and XhoI. The SacI-XhoI-fragment, carrying the expression cassette, was purified by electrophoresis on a 0.8% agarose gel, electroeluted (Sambrook et al., 1989), precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 4.8 and 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 12000 g for 30 min, washed with 70% ethanol, dried and then subjected to the action of Mung Bean nuclease enzyme (New England Biolabs) according to the manufacturer's recommendations. This purified insert (200 ng) was cloned into the plasmid DNA of pBIOC4 (20 ng) digested with EcoRI, treated with the Mung Bean nuclease enzyme and dephosphorylated with the enzyme calf intestinal alkaline phosphatase (Boehringer Mannheim) according to the manufacturer's recommendations. The ligation reaction was carried out in 20 .mu.l, in the presence of 2 .mu.l of 10.times.T4 DNA ligase buffer (Amersham), 2 .mu.l of 50% polyethylene glycol 8000 and 5 U of T4 DNA ligase enzyme (Amersham) at 14.degree. C. for 16 hours. The E. coli DH5.alpha. bacteria previously made competent were transformed (Hanahan, 1983). The plasmid DNA of the clones obtained, selected on 12 .mu.g/ml tetracyclin was extracted according to the alkaline lysis method (Birnboim and Doly, 1979) and analyzed by enzymatic digestion with restriction enzymes. The resulting plasmid was called pBIOC21.

Detailed Description Text - DETX:

The co-expression binary plasmid is derived from pBIOC21. It contains two expression cassettes each consisting of a pd35S promoter and a 35S polyA terminator but differ in the polylinker separating the promoter from the terminator. One of the expression cassettes is that of pBIOC21 already described in paragraph I.a. The other expression cassette was obtained by replacing the HindIII-BamHI-SmaI-EcoRI polylinker of pJIT163D (described in paragraph I.a.) by a HindIII-EcoRI adaptor carrying the PacI, AscI, MluI and HpaI restriction sites. This adaptor was obtained by renaturation of the 2 oligodeoxynucleotides WD 11 (5' AGC TGA TTA ATT AAG GCG CGC CAC GCG TTA AC 3'; SEQ ID NO: 1) and WD12 (5' AAT TGT TAA CGC GTG GCG CGC CTT AAT TAA TC 3'; SEQ ID NO: 2) which are complementary for their 28 terminal 3' nucleotides. One

hundred .mu.M of each of these two oligodeoxynucleotides were previously phosphorylated by the action of 10 U of T4 polynucleotide kinase enzyme (New England Biolabs) in a total reaction volume of 10 .mu.l of 10.times.T4 polynucleotides kinase buffer (New England Biolabs) and 3 .mu.l of ATP (95 mM). The two reaction mixtures were incubated at 37.degree. C. for 1 hour, and then at 65.degree. C. for 20 min. They were then combined and their volume of phenol;chloroform:isoamyl alcohol (25:24:1) and 1 volume of chloroform:isoamyl alcohol (24:1), 50 .mu.l of 3M sodium **acetate** pH 6.0 were added. The reaction mixture was incubated at 80.degree. C. for 10 min and then cooled slowly to room temperature. The DNA was then precipitated in the presence of 2.5 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 14000 g at 4.degree. C. for 1 hour, washed with 70% ethanol, centrifuged at 14000 g at 4.degree. C. for 10 min, dried, taken up in 10 .mu.l of H2O. The HindIII-EcoRI DNA fragment was then cloned at the HindIII-EcoRI sites of the plasmid DNA pJIT163D previously dephosphorylated with the enzyme calf intestinal alkaline phosphatase (New England Biolabs) according to the manufacturer's recommendations. The ligation reaction was carried out in a reaction volume of 20 .mu.l in the presence of 1 U of T4 DNA ligase (Gibco-BRL) for a total DNA concentration of 8.5 nM with a vector/insert molar ratio of 1 and of 4 .mu.l of 5.times.T4 DNA ligase buffer (Gibco-BRL) at 25.degree. C. for 16 hours. The E. coli DH5.alpha. bacteria previously made competent were transformed (Hanahan, 1985). The plasmid DNA of the clones obtained, selected on 100 .mu.g/ml ampicillin, was extracted according to the alkaline lysis method (Stephen et al., 1990) and analyzed by enzymatic digestion. The resulting clone was called pBIOC42. Its validity was verified by sequencing with the aid of the "Sequenase Version 2.0 DNA Sequencing" kit marketed by United States Biochemical (USB) according to the dideoxynucleotides method (Sanger et al., 1977). The reaction conditions follow the manufacturer's recommendations except for the denaturation and hybridization. The reaction medium containing the plasmid DNA (0.5 to 1 pmol), the oligonucleotide primer (2pmol), 10% DMSO and the 1.times. reaction buffer (USB), is incubated at 100.degree. C. for 10 min, then suddenly cooled to -80.degree. C. in dry ice.

Detailed Description Text - DETX:

The third stage was the PCR amplification of the complete cDNA encoding the .alpha. globin chain (142 codons including the initiator ATG). The two types of DNA fragments amplified in the first and second stages served as template DNA and the two primers used were WD13 and WD14. The PCR amplification was carried out as described in the first stage except that the hybridization temperature of the cycle is 60.degree. C. The amplified DNA fragments were then extracted with H.sub.2 O-saturated ether after having adjusted the volume to 500 .mu.l with TE buffer (10 mM Tris-HCl pH 8.0, 1 mM EDTA). After extraction with 1 volume of phenol:chloroform:isoamyl alcohol (25:24:1) and 1 volume of chloroform:isoamyl alcohol (24:1), the DNA fragments were precipitated in the presence of 1/10 volume of 3 M sodium **acetate** pH 6.0 and 2 volumes of absolute ethanol at -80.degree. C. for 30 min, centrifuged at 14000 g at 4.degree. C. for 30 min, washed with 70% ethanol, centrifuged at 14000 g at 4.degree. C. for 10 min, dried, taken up in 50 .mu.l of H.sub.2 O. Next, 25 .mu.l of these DNA fragments were doubly digested with HindIII and EcoRI, purified by electrophoresis on 1.8% agarose gel and by the action of the "Geneclean II" kit (BIO101) and cloned at the HindIII and EcoRI sites of the

plasmid pNEB193 marketed by New England Biolabs, and previously dephosphorylated with the enzyme calf intestinal alkaline phosphatase (New England Biolabs) according to the manufacturer's recommendations. The ligation and the transformation were carried out as described in section I.b. The plasmid DNA of the clones obtained, selected on 100 .mu.g/ml ampicillin, was extracted according to the alkaline lysis method (Stephen et al., 1990) and analyzed by enzymatic digestion. The resulting clone was called pBIOC44. The nucleotide sequence of the cDNA encoding the recombinant .alpha. globin chain was verified by sequencing with the aid of the "Sequenase Version 2.0 DNA Sequencing" kit marketed by United States Biochemical (USB) as described in section I.b. The sequencing revealed two silent mutations situated at the forty-eighth nucleotide (C modified to T) and at the fifty-fourth (T modified to C) of the coding sequence for the .alpha. globin chain.

Detailed Description Text - DETX:

To allow vacuolar targeting, the **sequence encoding the prepropeptide (PPS)** of sporamine A of the tuberized roots of sweet potato (Murakami et al., 1986; Matsuoka and Nakamura, 1991), which corresponds to the signal peptide followed by the N-terminal sequence for vacuolar targeting (ATG AAA GCC TTC ACA CTC GCT CTC TTC TTA GCT CTT TCC CTC TAT CTC CTG CCC AAT CCA GCC CAT TCC AGG TTC AAT CCC
ATC CGC CTC CCC ACC ACA CAC GAA CCC GCC; SEQ ID NO: 27), is fused with the first codon of the sequence encoding, on the one hand, the mature .alpha. globin chain (deletion of the initiator ATG) and, on the other hand, the mature .beta. globin chain (deletion of the initiator ATG) while maintaining the open reading frames. This prepropeptide of 37 amino acids was isolated from the plasmid pMAT103 (Matuoka and Nakamura, 1991) and used during the carrying out of the constructions.

US-PAT-NO: 6165767

DOCUMENT-IDENTIFIER: US 6165767 A

TITLE: Protein phosphatase-related molecules

DATE-ISSUED: December 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lal; Preeti	Santa Clara	CA	N/A	N/A
Yue; Henry	Sunnyvale	CA	N/A	N/A
Corley; Neil C.	Mountain View	CA	N/A	N/A
Guegler; Karl J.	Menlo Park	CA	N/A	N/A
Baughn; Mariah	San Jose	CA	N/A	N/A

APPL-NO: 09/ 045973

DATE FILED: March 20, 1998

US-CL-CURRENT: 435/196; 435/252.3 ; 435/320.1 ; 435/6 ; 435/69.1 ; 536/23.2 ; 536/23.5

ABSTRACT:

The invention provides human protein phosphatase-related molecules (PPRM) and polynucleotides which identify and encode PPRM. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of PPRM.

12 Claims, 18 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 18

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Brief Summary Text - BSTX:

There appear to be three evolutionarily-distinct protein phosphatase **gene families: protein phosphatases (PPs)**; protein tyrosine phosphatases (PTPs); and acid/alkaline phosphatases (APs). PPs dephosphorylate phosphoserine/threonine residues and are an important regulator of many cAMP-mediated hormone responses in cells. PTPs reverse the effects of protein tyrosine kinases and play a significant role in cell cycle and cell signaling processes. APs dephosphorylate substrates in vitro, although their role in vivo is not well

known.

Detailed Description Text - DETX:

The frozen tissue was homogenized and lysed using a Brinkmann Homogenizer Polytron PT-3000 (Brinkmann Instruments, Westbury, N.J.) in guanidinium isothiocyanate solution. The lysate was centrifuged over a 5.7 M CsCl cushion using an Beckman SW28 rotor in a Beckman L8-70M Ultracentrifuge (Beckman Instruments) for 18 hours at 25,000 rpm at ambient temperature. The RNA was extracted with acid phenol pH 4.7, precipitated using 0.3 M sodium **acetate** and 2.5 volumes of ethanol, resuspended in RNAse-free water, and treated with DNase at 37.degree. C. RNA extraction and precipitation were repeated as before. The mRNA was isolated with the Qiagen Oligotex kit (QIAGEN, Inc., Chatsworth, Calif.) and used to construct the cDNA library.

US-PAT-NO: 6043028

DOCUMENT-IDENTIFIER: US 6043028 A

TITLE: Method for synthesizing single-stranded stem-loop DNA's the products and uses therefore

DATE-ISSUED: March 28, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ohshima; Atsushi	Kyoto-fu	N/A	N/A	JP
Inouye; Sumiko	Bridgewater	NJ	N/A	N/A
Inouye; Masayori	Bridgewater	NJ	N/A	N/A

APPL-NO: 08/ 430277

DATE FILED: April 28, 1995

PARENT-CASE:

This application is a continuation of application Ser. No. 08/024,676 filed Mar. 1, 1993 now abandoned, which is a CIP of Ser. No. 07/753,111 Aug. 30, 1991, now abandoned.

US-CL-CURRENT: 435/6; 435/91.1 ; 435/91.4 ; 435/91.5 ; 536/22.1 ; 536/24.5

ABSTRACT:

A method of synthesis of new and useful single-stranded DNAs which have a stem-loop configuration (ss-slDNA). The method is an in vivo or an in vitro synthesis. Replicating vehicles which produce these ss-slDNAs. The ss-slDNAs are described. Uses for these slDNAs are disclosed. They can be used for introducing random mutations, they lend themselves for replication by a variant of the PCR method. They can also be used for regulating gene function. Other uses are disclosed.

33 Claims, 32 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 19

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Detailed Description Text - DETX:

The slDNA prepared in Example 10-2 were labeled with [.gamma.-.sup.32 P]ATP by

phosphorylation. Triple helix formation was made by mixing radiolabeled slDNA and excess target DNA in a 0.15M NaCl/10 mM MgCl.sub.2 /5 mM tris-**acetate** (pH7.0) buffer, and then incubated at 37.degree. C. overnight. Triple helix formation was detected by 12% polyacrylamide gel electrophoresis in 50 mM tris-borate/5 mM MgCl.sub.2 (pH8.3) buffer.

Detailed Description Text - DETX:

Saccharomyces cerevisiae YPH499 cells (Stratagene) were transformed by pYES2-8-106 or pYES2-9-106 by the LiAc procedure [see Journal of Bacteriology, 153, 163-168, (1983)]. These transformants were grown on 100 ml of YPD medium (1% yeast extract, 2% bacto-peptone, 2% dextrose) to an OD.sub.600 of approximately 1.5. The cells were harvested by centrifugation, and washed once with 10 ml of SCE solution (182 g/l Sorbitol, 29.4 g/l Na.sub.2 Citrate, 22.3 g/l Na.sub.2 EDTA). Next, the cells were suspended in solution I (SCE solution containing 0.1% .beta.-mercaptoethanol and 0.5 mg/ml Zymolyase 100T) and shaken gently at 37.degree. C. for 2 hours to generate spheroplasts. Next, 8 ml of solution II (0.2 N NaOH, 1% SDS) was added and the suspensions were held on ice for 5 minutes. Next, 6 ml of solution III (60 ml of 5M K-**acetate,** 11.5 ml of glacial acetic acid, 28.5 ml of H.sub.2 O) was added, held on ice for additional 5 minutes, and then centrifuged. The DNAs were precipitated by addition of isopropanol to the supernatants, washed with 70% ethanol, and resuspended in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH7.6). The DNAS were further purified by phenol/chloroform extraction, ethanol precipitation, and using Qiagen tip 5 (Qiagen Inc.). Finally the purified DNA were suspended in 20 .mu.l of TE buffer.

Detailed Description Text - DETX:

Palindromes have been defined to include inverted repetitious sequences in which almost the same (not necessarily the same) sequences run in opposite direction. Though some are short (3-10 bases in one direction), others are much longer, comprising hundreds of base pairs. Watson, Molecular Biology of the **Gene, 3rd Ed., pps**. 224-225.

US-PAT-NO: 5985617

DOCUMENT-IDENTIFIER: US 5985617 A

TITLE: Microorganisms and methods for overproduction of DAHP by cloned **PPS gene**

DATE-ISSUED: November 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liao; James C.	Los Angeles	CA	90024	N/A

APPL-NO: 09/ 277183

DATE FILED: March 26, 1999

PARENT-CASE:

This is a Continuation of U.S. patent application Ser. No. 08/801,454 filed on Feb. 18, 1997 U.S. Pat. No. 5,906,925.

US-CL-CURRENT: 435/72; 435/108 ; 435/200 ; 536/23.7 ; 536/24.1

ABSTRACT:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The overexpression of phosphoenol pyruvate synthase increases DAHP production to near theoretical yields.

29 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

TITLE - TI:

Microorganisms and methods for overproduction of DAHP by cloned **PPS gene**

Abstract Text - ABTX:

Genetic elements comprising expression vectors and a **gene coding for**

phosphoenol pyruvate synthase is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The overexpression of phosphoenol pyruvate synthase increases DAHP production to near theoretical yields.

Brief Summary Text - BSTX:

The present invention provides genetically engineered strains of microorganisms that overexpress the **pps gene** for increasing the production of DAHP to near theoretical yields. The present invention also provides genetically engineered strains of microorganisms where at least one of the plasmids pPS341, pPSL706, pPS706, or derivatives thereof is transformed into a microorganism for increasing the production of DAHP to near theoretical yields.

Brief Summary Text - BSTX:

The present invention further provides a method for increasing carbon flow for the biosynthesis of DAHP in a host cell comprising the steps of transforming into the host cell recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced levels relative to wild type host cells, concentrating the transformed cells through centrifugation, resuspending the cells in a minimal, nutrient lean medium, fermenting the resuspended cells, and isolating DAHP from the medium.

Brief Summary Text - BSTX:

The present invention further provides methods of increasing carbon flow into the common aromatic pathway of a host cell comprising the step of transforming the host cell with recombinant DNA comprising a **pps gene so that Pps** is expressed at appropriate point in the metabolic pathways at enhanced levels relative to wild type host cells.

Brief Summary Text - BSTX:

The present invention further provides a genetic element comprising a **pps gene** and one or more genes selected from the group consisting of an aroF gene, aroG gene, aroH gene, and an aroB gene.

Brief Summary Text - BSTX:

The present invention further provides a DNA molecule comprising a vector carrying a **gene coding for Pps**.

Detailed Description Text - DETX:

The inventor have found that cell lines can be developed that increase the carbon flux into DAHP production and achieve near theoretical yields of DAHP by

overexpressing phosphoenolpyruvate synthase (Pps) in the cell lines. Overexpression of Pps can increase the final concentration and yield of DAHP by as much as two-fold, to a near theoretical maximum as compared to wild type cell lines. The overexpression of Pps is achieved by transforming a cell line with recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced level relative to the wild type cell line and so that the yield of DAHP approaches its theoretical value.

Detailed Description Text - DETX:

Besides the use of the **pps gene,** the present invention also provides for transfer of genetic elements comprising the tkt gene, the gene coding for DAHP synthase (aroF in E. coli), the gene coding for 3-dehydroquinate synthase (aroB in E. coli), or other genes encoding enzymes that catalyze reactions in the common aromatic pathway. Such a cell transformation can be achieved by transferring one or more plasmids that contain genes that code for enzymes that increase the carbon flux for DAHP synthesis and for subsequent synthesis of other desired cyclic, pre-aromatic, and aromatic metabolites. As a result of this transfer of genetic element(s), more carbon enters and moves through the common aromatic pathway relative to wild type host cells not containing the genetic elements of the present invention.

Detailed Description Text - DETX:

In one embodiment, the present invention comprises a method for increasing carbon flow into the common aromatic pathway of a host cell by increasing the production of DAHP through the overexpression of Pps at the appropriate point in the common aromatic pathway to provide additional PEP at the point where PEP condenses with E4P. Increasing carbon flow requires the step of transforming the host cell with recombinant DNA containing a **pps genes so that Pps** is overexpressed at enhanced levels relative to wild type host cells. DAHP is then produced by fermentation of the transformed cell in a nutrient medium which the DAHP can be extracted from the medium on a batch wise or continuous extraction procedure.

Detailed Description Text - DETX:

In another embodiment, the present invention involves the co-overexpression of a **pps gene** and other genes coding for enzymes of the common aromatic pathway where additional genetic material is transformed into the host cell. The genes transferred can include the tkt gene, DAHP synthase gene and DHQ synthase gene (preferably the aroF or aroB genes, respectively). Although the work so far has centered around transforming certain host cell strains of E. coli such as AB2847 aroB, this particular host cell may not be the preferred host cell for the commercial production of DAHP or DAHP metabolites through the overexpression of Pps.

Detailed Description Text - DETX:

Another embodiment of the present invention is a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway. This method involves the step of increasing expression of Pps in the host cell relative to a wild type host cell. The step of increasing expression of Pps can include transferring into the host cell a vector carrying the **pps gene**. The overexpression of Pps results in forcing increased carbon flow into the biosynthesis of DAHP.

Detailed Description Text - DETX:

In another embodiment of the present invention, a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway relative to wild type host cell's biosynthetic production of such compound is provided. This method requires the step of increasing expression in a host cell of a protein catalyzing conversion of pyruvate to PEP. The expression of such a protein can involve transferring into the host cell recombinant DNA including a **pps gene**.

Detailed Description Text - DETX:

In another preferred embodiment, the present invention comprises a genetic element comprising the **pps gene** and a gene selected from the group consisting of a aroF gene, a aroB gene, and a tkt gene. Such a genetic element can comprise plasmid pPS341, a vector carrying a **pps gene**.

Detailed Description Text - DETX:

In previous work, the inventor demonstrated that overexpression of Pps in host cells cultured on nutrient rich, glucose containing medium led to growth inhibition, increased glucose consumption, and excretion of pyruvate and **acetate**. Their previous study also showed that the effects of Pps overexpression on DAHP production, in actively growing cultures, are not as significant, and that the adverse effects of Pps overexpression on cell growth negated any beneficial effects on DAHP production.

Detailed Description Text - DETX:

PEP is also a precursor to the pathways that utilize the enzyme phosphoenol pyruvate carboxylase (Ppc) coded by the ppc gene. It has been reported that the deletion of ppc increased the production of phenylalanine and **acetate**. Moreover, it has been shown that the overexpression of Ppc in a wild-type host reduces **acetate** production. Both results may indicate that the flux through Ppc (from PEP to OAA) is reasonably significant under those conditions, and thus, the modulation of Ppc expression level may affect the utilization of PEP. However, in the present invention, deleting the chromosomal ppc gene did not have a positive effect on DAHP production, suggesting that the flux through Ppc is not important in the methods of the present invention.

Detailed Description Text - DETX:

One preferred embodiment of the present invention encompasses modification of a host cell to cause overexpression of an enzyme having the catalytic properties of naturally derived Pps, and, thereby maximizing the yield of DAHP to near theoretical yields. Enzymes having the catalytic activity of Pps include, but are not limited to, Pps produced by expression in whole cells of a naturally derived **pps gene,** enzymes produced by expression in whole cells of a naturally derived **pps gene** modified by sequence deletion or addition so that the expressed enzyme has an amino acid **sequence that varies from unmodified Pps,** abzymes produced to have catalytic sites with steric and electronic properties corresponding to catalytic sites of Pps, or other proteins produced to have the capability of catalyzing the conversion of pyruvate to PEP by any other art recognized means.

Detailed Description Text - DETX:

Additionally, the transformation of DNA, including the **pps gene,** into microorganisms engineered for the overexpression of other substrates, and/or overexpression or derepression of enzymes in the pentose phosphate or common aromatic pathway can be used to tailor the microorganism to achieve near theoretical yields of such DAHP metabolites as tyrosine, tryptophan, phenylalanine, and other aromatic metabolites such as indigo, catechol and quinoid organics such as quinic acid, benzoquinone, and hydroquinone.

Detailed Description Text - DETX:

Plasmid pPS341 was constructed by cloning a fragment of E. coli chromosomal DNA containing **pps gene** into an IPTG-inducible expression vector pUHE23-2 (a pBR322 derivative) as taught by Patnaik et al., (Patnaik, R., W. D. Roof, R. F. Young, and J. C. Liao, "Stimulation of Glucose Catabolism in Escherichia coli by a Potential Futile Cycle," J. Bacteriology 1992, 174: 7527-7532) and the contents of which are herein incorporated by reference. Plasmid pPS341X1 containing the inactive **gene product of pps** was constructed by codon insertion mutagenesis, the details of which are fully described in Patnaik et al. (Castilho, B. A., P. Olfson, and M. J. Casadaban, "Plasmid Insertion Mutagenesis and lac Gene Fusion with Mini-Mu Bacteriophage Transposons," J. Bacteriology. 1984, 158: 488-495). The **pps gene** on pPS341 was inserted with a Mu dll1734 lac.sup.+ Km.sup.r (MudK) according to published protocol of Castiho et al., the contents of which are herein incorporated by reference. Briefly, a Mu lysate was made from a donor strain POll1734/pPS341, which was lysogenized by the mini-Mu element and a Mu cts. The lysate was used to infect a Mu lysogen of HG4 pps pck, and colonies were selected for Ap.sup.r and Km.sup.r simultaneously to ensure that the mini-Mu element hopped to the plasmid. Colonies were further screened for Pps.sup.- phenotype (inability to grow on pyruvate). Restriction analysis of plasmid DNA further confirmed the insertion of the MudK element into the **pps gene** on plasmid pPS341. 20% of these selected colonies showed IPTG-dependent expression of .beta.-galactosidase, indicating an in-frame insertion. The plasmid from one such colony was named pPS1734, which was then linearized at the Scal site, and transformed into strain JC7623 recB21 recC22 sbcB15.

Transformants were selected for Km.sup.r and scored for Ap sensitivity. Such colonies presumably contained pps::MudK on the chromosome. By use of P1 transduction, this locus was moved to AB2847 and Km.sup.r transductants were further screened for inability to grow on pyruvate. One such colony was designated JCL1362 and used for later studies. The MudK insertion into chromosomal pps was further confirmed by cotransduction frequency (89%) with Tet.sup.r marker from strain CAG12151 zdh-925::Tn10.

Detailed Description Text - DETX:

The plasmid pPS706 was constructed by inserting a 2.4 kb PCR fragment containing the promoter-less **pps gene** into the vector pJF118EH. The primers were designed from the published **pps sequence** and contained an EcoRI site and a .phi.10 ribosome binding site upstream of the **pps sequence** and a BamHI site downstream of the sequence. The PCR product was then cloned into the EcoRI and BamHI sites of pJF118EH. Positive clones were selected based on complementation of HG4 pps for growth on pyruvate. Expression of pps from this construct is controlled by the tac promoter inducible by IPTG.

Detailed Description Text - DETX:

The plasmid pPSL706 was then constructed from pPS706 as shown in FIG. 5. Briefly, a ScaI/EcoRI fragment containing the **pps gene** was cut from pPS706 and purified from the restriction buffer. This fragment was then cloned into a purified ScaI-EcoRI fragment containing the luxI' promoter from pGS103, kindly given to the inventor by Tom Baldwin. Department of Biochemistry and Biophysics, Texas A&M University. Expression using this system is controlled by the autoinducer (AI) in the culture media. pPSL706 is ampicillin resistant and compatible with other pACYC184 derivatives such as pRW5 and pATI. The strains and plasmids used are summarized in Table I and Table II.

Detailed Description Text - DETX:

To gain insight into the metabolic flux distribution, the culture broth was analyzed for fermentation byproducts by use of HPLC. Samples were taken from cultures in glucose media with varying activities of Pps, AroG, and TktA. Results indicate that the host strain AB2847 produced **acetate,** succinate, and formate as the major byproducts when neither AroG nor Pps was overexpressed. Production of these acids generally decreased with the increase in IPTG concentration, except formate. This decrease correlates with the increase in DAHP production. When AB2847/pAT1/pPS706 was cultured in glucose with IPTG concentration beyond 50 mM, the broth had undetectable levels of these acids (data not shown). While levels of formic and acetic acid decreased with increase in Pps activity, succinic acid either remained constant (0 .mu.M IPTG) or increased (10.50 .mu.M IPTG) with an increase in Pps activity. This increase could be contributed to Pps induced increase in PEP level, which is spilled over through PEP carboxylase and eventually to succinate.

Detailed Description Text - DETX:

This example demonstrates that the E. coli AB2847 is unable to utilize DAHP, and accumulates DAHP in the medium if DAHP synthase is overexpressed. This strain was used as a host for detecting the flux committed to the aromatic pathways. Since Draths et al. (Draths, K. M., D. L. Pompliano, D. L. Conley, J. W. Frost, A. Berry, G. L. Disbrow, R. J. Staversky, and J. C. Lievense, "Biocatalytic synthesis of aromatics from D-glucose: The role of transketolase," J. Am. Chem. Soc., 1992, 114, 3956-3962) have shown a possible limitation in the production of DAHP by E4P, pAT1 (containing both aroG.sup.fbr and tktA) was transformed into AB2847 to eliminate the limitation of E4P. To test whether PEP supply limits DAHP production, PEP synthase (Pps) was overexpressed in AB2847/pAT1 by transforming plasmid pPS341 into this strain. 20-70 copies of the **pps gene** were expressed in the host cells. As a control, pPS341 was substituted by pPS341X1, which encodes an inactive, but stable **pps gene** product. The use of the inactive Pps control allowed discrimination between the effect of Pps activity and that of protein overexpression. AB2847/pAT1/pUHE23-2 and AB2847/pAT1 were also used without any other plasmid as additional controls to identify the effect of the cloning vector, pUHE23-2, on DAHP production.

Detailed Description Text - DETX:

As shown above, Pps overexpression improved DAHP production from glucose. To determine whether the basal level of pps expression in glucose medium contributed to the production of DAHP, the chromosomal **pps gene** in strain AB2847 was knocked out. The resulting strain (JCL1362) was used as the host to repeat the above experiments. Results show that inactivation of chromosomal pps did not significantly affect the DAHP production in strains containing pRW5 or pAT1 (FIG. 2B). Therefore, the basal level of pps expression in glucose medium did not contribute to the DAHP production.

Detailed Description Text - DETX:

To produce tryptophan, strain ATCC31743 which contains chromosomal markers such as trpR .DELTA.(trpAE) tna can be used as a host. This strain also contains a plasmid pSC102trp which harbors trpAE operon. Plasmids pATI and pPS341 (or pPS706 or pPSL706) can be transformed into this strain. The serA gene can be cloned into any of the plasmids. Alternatively, these cloned **genes (trpAE, aroG, tktt, pps** or serA) can be consolidated to one or two plasmids. The resulting strain was grown in MT medium which contains, per liter: KH.sub.2 PO.sub.4, 3 g; K.sub.2 HPO.sub.4, 3 g; K.sub.2 HPO.sub.4, 7 g; NH.sub.4 CL, 3 g; MgSO.sub.4, 0.2 g; FeSO.sub.4 (7H.sub.2 O), 10 mg; glucose, 0 to 30 g.

Detailed Description Text - DETX:

Quinoid organics can be derived from dehydroquinate which is a down-stream metabolite of DAHP. To produce quinic acid, E. coli AB2848 aroD harboring pTW8090A which contains the gene qad (quinic acid dehydrogenase from Klebsiella pneumoniae) (ref: Draths, Ward, and Frost, 1992, JACS, 114, 9725-9726), and pKD136 (ref: same as above) which contains tkt, aroF, and aroB genes can be

used as a host. The **pps gene** can be cloned into one of these plasmids and be simultaneously overexpressed. It has been reported that at least 80 mM of D-glucose can be converted into 25 mM of quinic acid. After cell removal, quinic acid in the supernatant can be converted into benzoquinone after addition of sulfuric acid and technical grade manganese (IV) dioxide and heating at 100.degree. C. for 1 h. In the absence of acidification, aqueous solutions of purified quinic acid are converted to hydroquinone in 10% yield upon heating at 100.degree. C. for 18 h with technical grade manganese dioxide.

Claims Text - CLTX:

(a) placing a microorganism with genetic elements comprising **pps and tkt genes** wherein said genes are expressed by said microorganism in a media comprising glucose solution;

Claims Text - CLTX:

(b) overexpressing the **pps and tkt genes** of said microorganisms in the glucose media; and

Claims Text - CLTX:

3. The method of claim 1 wherein the **pps gene** is operably linked to a tac promoter.

Claims Text - CLTX:

(a) placing a microorganism with genetic elements comprising **pps, tkt, and serA genes** wherein said genes are expressed by said microorganism in a media comprising glucose solution;

Claims Text - CLTX:

(b) overexpressing the **pps, tkt, and serA genes** of said microorganisms in the glucose media; and

Claims Text - CLTX:

10. The method of claim 8 wherein the **pps gene** is operably linked to a tac promoter.

Claims Text - CLTX:

(a) placing a microorganism with genetic elements comprising **pps, tkt, and**

pheA.sup.fbr genes wherein said genes are expressed by said microorganism in a media comprising glucose solution;

Claims Text - CLTX:

(b) overexpressing the **pps, tkt, and pheA.sup.fbr genes** in said microorganisms in said glucose media; and

Claims Text - CLTX:

17. The method of claim 15 wherein the **pps gene** is operably linked to a tac promoter.

Claims Text - CLTX:

(a) placing a microorganism with genetic elements comprising **pps, tkt, and qad genes** wherein said genes are expressed by said microorganism in a media comprising glucose solution;

Claims Text - CLTX:

(b) overexpressing the **pps, tkt, and qad genes** in said microorganisms in the glucose media; and

Claims Text - CLTX:

24. The method of claim 22 wherein the **pps gene** is operably linked to a tac promoter.

US-PAT-NO: 5906925

DOCUMENT-IDENTIFIER: US 5906925 A

TITLE: Microorganisms and methods for overproduction of DAHP by cloned **pps gene**

DATE-ISSUED: May 25, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Liao; James C.	N/A	N/A	N/A	N/A
	College Station	TX	77843-312 2	

APPL-NO: 08/ 801454

DATE FILED: February 18, 1997

PARENT-CASE:

This application is a continuation of application Ser. No. 08/307,371, filed Sep. 16, 1994, now abandoned.

US-CL-CURRENT: 435/72; 435/108 ; 435/200 ; 536/23.7 ; 536/24.1

ABSTRACT:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The overexpression of phosphoenol pyruvate synthase increases DAHP production to near theoretical yields.

28 Claims, 14 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

TITLE - TI:

Microorganisms and methods for overproduction of DAHP by cloned **pps gene**

Abstract Text - ABTX:

Genetic elements comprising expression vectors and a **gene coding for phosphoenol pyruvate synthase** is utilized to enhance diversion of carbon resources into the common aromatic pathway and pathways branching therefrom. The overexpression of phosphoenol pyruvate synthase increases DAHP production to near theoretical yields.

Brief Summary Text - BSTX:

The present invention provides genetically engineered strains of microorganisms that overexpress the **pps gene** for increasing the production of DAHP to near theoretical yields. The present invention also provides genetically engineered strains of microorganisms where at least one of the plasmids pPS341, pPSL706, pPS706, or derivatives thereof is transformed into a microorganism for increasing the production of DAHP to near theoretical yields.

Brief Summary Text - BSTX:

The present invention further provides a method for increasing carbon flow for the biosynthesis of DAHP in a host cell comprising the steps of transforming into the host cell recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced levels relative to wild type host cells, concentrating the transformed cells through centrifugation, resuspending the cells in a minimal, nutrient lean medium, fermenting the resuspended cells, and isolating DAHP from the medium.

Brief Summary Text - BSTX:

The present invention further provides methods of increasing carbon flow into the common aromatic pathway of a host cell comprising the step of transforming the host cell with recombinant DNA comprising a **pps gene so that Pps** is expressed at appropriate point in the metabolic pathways at enhanced levels relative to wild type host cells.

Brief Summary Text - BSTX:

The present invention further provides a genetic element comprising a **pps gene** and one or more genes selected from the group consisting of an aroF gene, aroG gene, aroH gene, and an aroB gene.

Brief Summary Text - BSTX:

The present invention further provides a DNA molecule comprising a vector carrying a **gene coding for Pps**.

Detailed Description Text - DETX:

The inventor have found that cell lines can be developed that increase the carbon flux into DAHP production and achieve near theoretical yields of DAHP by overexpressing phosphoenolpyruvate synthase (Pps) in the cell lines. Overexpression of Pps can increase the final concentration and yield of DAHP by as much as two-fold, to a near theoretical maximum as compared to wild type cell lines. The overexpression of Pps is achieved by transforming a cell line with recombinant DNA comprising a **pps gene so that Pps** is expressed at enhanced level relative to the wild type cell line and so that the yield of DAHP approaches its theoretical value.

Detailed Description Text - DETX:

Besides the use of the **pps gene,** the present invention also provides for transfer of genetic elements comprising the tkt gene, the gene coding for DAHP synthase (aroF in E. coli), the gene coding for 3-dehydroquinate synthase (aroB in E. coli), or other genes encoding enzymes that catalyze reactions in the common aromatic pathway. Such a cell transformation can be achieved by transferring one or more plasmids that contain genes that code for enzymes that increase the carbon flux for DAHP synthesis and for subsequent synthesis of other desired cyclic, pre-aromatic, and aromatic metabolites. As a result of this transfer of genetic element(s), more carbon enters and moves through the common aromatic pathway relative to wild type host cells not containing the genetic elements of the present invention.

Detailed Description Text - DETX:

In one embodiment, the present invention comprises a method for increasing carbon flow into the common aromatic pathway of a host cell by increasing the production of DAHP through the overexpression of Pps at the appropriate point in the common aromatic pathway to provide additional PEP at the point where PEP condenses with E4P. Increasing carbon flow requires the step of transforming the host cell with recombinant DNA containing a **pps gene so that Pps** is overexpressed at enhanced levels relative to wild type host cells. DAHP is then produced by fermentation of the transformed cell in a nutrient medium from which the DAHP can be extracted from the medium on a batch wise or continuous extraction procedure.

Detailed Description Text - DETX:

In another embodiment, the present invention involves the co-overexpression of a **pps gene** and other genes coding for enzymes of the common aromatic pathway where additional genetic material is transformed into the host cell. The genes transferred can include the tkt gene, DAHP synthase gene and DHQ synthase gene (preferably the aroF or aroB genes, respectively). Although the work so far has centered around transforming certain host cell strains of E. coli such as AB2847 aroB, this particular host cell may not be the preferred host cell for the commercial production of DAHP or DAHP metabolites through the overexpression of Pps.

Detailed Description Text - DETX:

Another embodiment of the present invention is a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway. This method involves the step of increasing expression of Pps in the host cell relative to a wild type host cell. The step of increasing expression of Pps can include transferring into the host cell a vector carrying the **pps gene**. The overexpression of Pps results in forcing increased carbon flow into the biosynthesis of DAHP.

Detailed Description Text - DETX:

In another embodiment of the present invention, a method for enhancing a host cell's biosynthetic production of compounds derived from the common aromatic pathway relative to wild type host cell's biosynthetic production of such compound is provided. This method requires the step of increasing expression in a host cell of a protein catalyzing conversion of pyruvate to PEP. The expression of such a protein can involve transferring into the host cell recombinant DNA including a **pps gene**.

Detailed Description Text - DETX:

In another preferred embodiment, the present invention comprises a genetic element comprising the **pps gene** and a gene selected from the group consisting of a aroF gene, a aroB gene, and a tkt gene. Such a genetic element can comprise plasmid pPS341, a vector carrying a **pps gene**.

Detailed Description Text - DETX:

In previous work, the inventor demonstrated that overexpression of Pps in host cells cultured on nutrient rich, glucose containing medium led to growth inhibition, increased glucose consumption, and excretion of pyruvate and **acetate**. Their previous study also showed that the effects of Pps overexpression on DAHP production, in actively growing cultures, are not as significant, and that the adverse effects of Pps overexpression on cell growth negated any beneficial effects on DAHP production.

Detailed Description Text - DETX:

PEP is also a precursor to the pathways that utilize the enzyme phosphoenol-pyruvate carboxylase (Ppc) coded by the ppc gene. It has been reported that the deletion of ppc increased the production of phenylalanine and **acetate**. Moreover, it has been shown that the overexpression of Ppc in a wild-type host reduces **acetate** production. Both results may indicate that the flux through Ppc (from PEP to OAA) is reasonably significant under those conditions, and thus, the modulation of Ppc expression level may affect the utilization of PEP. However, in the present invention, deleting the chromosomal ppc gene did not have a positive effect on DAHP production, suggesting that the flux through Ppc is not important in the methods of the

present invention.

Detailed Description Text - DETX:

One preferred embodiment of the present invention encompasses modification of a host cell to cause overexpression of an enzyme having the catalytic properties of naturally derived Pps, and, thereby maximizing the yield of DAHP to near theoretical yields. Enzymes having the catalytic activity of Pps include, but are not limited to, Pps produced by expression in whole cells of a naturally derived **pps gene,** enzymes produced by expression in whole cells of a naturally derived **pps gene** modified by sequence deletion or addition so that the expressed enzyme has an amino acid **sequence that varies from unmodified Pps,** abzymes produced to have catalytic sites with steric and electronic properties corresponding to catalytic sites of Pps, or other proteins produced to have the capability of catalyzing the conversion of pyruvate to PEP by any other art recognized means.

Detailed Description Text - DETX:

Additionally, the transformation of DNA, including the **pps gene,** into microorganisms engineered for the overexpression of other substrates, and/or overexpression or derepression of enzymes in the pentose phosphate or common aromatic pathway can be used to tailor the microorganism to achieve near theoretical yields of such DAHP metabolites as tyrosine, tryptophan, phenylalanine, and other aromatic metabolites such as indigo, catechol and quinoid organics such as quinic acid, benzoquinone, and hydroquinone.

Detailed Description Text - DETX:

Plasmid pPS341 was constructed by cloning a fragment of E. coli chromosomal DNA containing **pps gene** into an IPTG-inducible expression vector pUHE23-2 (a pBR322 derivative) as taught by Patnaik et al., (Patnaik, R., W. D. Roof, R. F. Young, and J. C. Liao, "Stimulation of Glucose Catabolism in Escherichia coli by a Potential Futile Cycle," J. Bacteriology 1992, 174: 7527-7532) and the contents of which are herein incorporated by reference. Plasmid pPS341X1 containing the inactive **gene product of pps** was constructed by codon insertion mutagenesis, the details of which are fully described in Patnaik et al. The **pps gene** on pPS341 was inserted with a Mu dII1734 lac.sup.+ Km.sup.r (MudK) according to published protocol of Castiho et al., (Castilho, B. A., P. Olfson, and M. J. Casadaban, "Plasmid Insertion Mutagenesis and lac Gene Fusion with Mini-Mu Bacteriophage Transposons," J. Bacteriology. 1984, 158: 488-495) the contents of which are herein incorporated by reference. Briefly, a Mu lysate was made from a donor strain POII1734/pPS341, which was lysogenized by the mini-Mu element and a Mu cts. The lysate was used to infect a Mu lysogen of HG4 pps pck, and colonies were selected for Apr and Km.sup.r simultaneously to ensure that the mini-Mu element hopped to the plasmid. Colonies were further screened for Pps.sup.- phenotype (inability to grow on pyruvate). Restriction analysis of plasmid DNA further confirmed the insertion of the MudK element into the **pps gene** on plasmid pPS341. 20% of these selected colonies showed IPTG-dependent

expression of .beta.-galactosidase, indicating an in-frame insertion. The plasmid from one such colony was named pPS1734, which was then linearized at the ScaI site, and transformed into strain JC7623 recB21 recC22 sbcB15. Transformants were selected for Km.sup.r and scored for Ap sensitivity. Such colonies presumably contained pps::MudK on the chromosome. By use of P1 transduction, this locus was moved to AB2847 and Km.sup.r transductants were further screened for inability to grow on pyruvate. One such colony was designated JCL1362 and used for later studies. The MudK insertion into chromosomal pps was further confirmed by cotransduction frequency (89%) with Tet.sup.r marker from strain CAG12151 zdh-925::Tn10.

Detailed Description Text - DETX:

The plasmid pPS706 was constructed by inserting a 2.4 kb PCR fragment containing the promoter-less **pps gene** into the vector pJF118EH. The primers were designed from the published **pps sequence** and contained an EcoRI site and a .phi.10 ribosome binding site upstream of the **pps sequence** and a BamHI site downstream of the sequence. The PCR product was then cloned into the EcoRI and BamHI sites of pJF118EH. Positive clones were selected based on complementation of HG4 pps for growth on pyruvate. Expression of pps from this construct is controlled by the tac promoter inducible by IPTG.

Detailed Description Text - DETX:

The plasmid pPSL706 was then constructed from pPS706 as shown in FIG. 5. Briefly, a ScaI/EcoRI fragment containing the **pps gene** was cut from pPS706 and purified from the restriction buffer. This fragment was then cloned into a purified ScaI-EcoRI fragment containing the luxI' promoter from pGS103, kindly given to the inventor by Tom Baldwin. Department of Biochemistry and Biophysics, Texas A&M University. Expression using this system is controlled by the autoinducer (AI) in the culture media. pPSL706 is ampicillin resistant and compatible with other pACYC184 derivatives such as pRW5 and pATI. The strains and plasmids used are summarized in Table I and Table II.

Detailed Description Text - DETX:

To gain insight into the metabolic flux distribution, the culture broth was analyzed for fermentation byproducts by use of HPLC. Samples were taken from cultures in glucose media with varying activities of Pps, AroG, and TktA. Results indicate that the host strain AB2847 produced **acetate,** succinate, and formate as the major byproducts when neither AroG nor Pps was overexpressed. Production of these acids generally decreased with the increase in IPTG concentration, except formate. This decrease correlates with the increase in DAHP production. When AB2847/pAT1/pPS706 was cultured in glucose with IPTG concentration beyond 50 mM, the broth had undetectable levels of these acids (data not shown). While levels of formic and acetic acid decreased with increase in Pps activity, succinic acid either remained constant (0 .mu.M IPTG) or increased (10.50 .mu.M IPTG) with an increase in Pps activity. This increase could be contributed to Pps induced increase in PEP level, which is spilled over through PEP carboxylase and eventually to succinate.

Detailed Description Text - DETX:

This example demonstrates that the E. coli AB2847 is unable to utilize DAHP, and accumulates DAHP in the medium if DAHP synthase is overexpressed. This strain was used as a host for detecting the flux committed to the aromatic pathways. Since Draths et al. (Draths, K. M., D. L. Pompliano, D. L. Conley, J. W. Frost, A. Berry, G. L. Disbrow, R. J. Staversky, and J. C. Lievense, "Biocatalytic synthesis of aromatics from D-glucose: The role of transketolase," J. Am. Chem. Soc., 1992, 114, 3956-3962) have shown a possible limitation in the production of DAHP by E4P, pAT1 (containing both aroG.sup.fbr and tktA) was transformed into AB2847 to eliminate the limitation of E4P. To test whether PEP supply limits DAHP production, PEP synthase (Pps) was overexpressed in AB2847/pAT1 by transforming plasmid pPS341 into this strain. 20-70 copies of the **pps gene** were expressed in the host cells. As a control, pPS341 was substituted by pPS341X1, which encodes an inactive, but stable **pps gene** product. The use of the inactive Pps control allowed discrimination between the effect of Pps activity and that of protein overexpression. AB2847/pAT1/pUHE23-2 and AB2847/pAT1 were also used without any other plasmid as additional controls to identify the effect of the cloning vector, pUHE23-2, on DAHP production.

Detailed Description Text - DETX:

As shown above, Pps overexpression improved DAHP production from glucose. To determine whether the basal level of pps expression in glucose medium contributed to the production of DAHP, the chromosomal **pps gene** in strain AB2847 was knocked out. The resulting strain (JCL1362) was used as the host to repeat the above experiments. Results show that inactivation of chromosomal pps did not significantly affect the DAHP production in strains containing pRW5 or pAT1 (FIG. 2B). Therefore, the basal level of pps expression in glucose medium did not contribute to the DAHP production.

Detailed Description Text - DETX:

To produce tryptophan, strain ATCC31743 which contains chromosomal markers such as trpR .DELTA.(trpAE) tna can be used as a host. This strain also contains a plasmid pSC102trp which harbors trpAE operon. Plasmids pATI and pPS341 (or pPS706 or pPSL706) can be transformed into this strain. The SerA gene can be cloned into any of the plasmids. Alternatively, these cloned **genes (trpAE, aroG, tktt, pps** or serA) can be consolidated to one or two plasmids. The resulting strain was grown in MT medium which contains, per liter: KH.sub.2 PO.sub.4, 3 g; K.sub.2 HPO.sub.4, 3 g; K.sub.2 HPO.sub.4, 7 g; NH.sub.4 CL, 3 g; MgSO.sub.4, 0.2 g; FeSO.sub.4 (7H.sub.2 O), 10 mg; glucose, 0 to 30 g.

Detailed Description Text - DETX:

Quinoid organics can be derived from dehydroquinate which is a down-stream metabolite of DAHP. To produce quinic acid, E. coli AB2848 aroD harboring

pTW8090A which contains the gene qad (quinic acid dehydrogenase from Klebsiella pneumoniae) (ref: Draths, Ward, and Frost, 1992, JACS, 114, 9725-9726), and pKD136 (ref: same as above) which contains tkt, aroF, and aroB genes can be used as a host. The **pps gene** can be cloned into one of these plasmids and be simultaneously overexpressed. It has been reported that at least 80 mM of D-glucose can be converted into 25 mM of quinic acid. After cell removal, quinic acid in the supernatant can be converted into benzoquinone after addition of sulfuric acid and technical grade manganese (IV) dioxide and heating at 100.degree. C. for 1 h. In the absence of acidification, aqueous solutions of purified quinic acid are converted to hydroquinone in 10% yield upon heating at 100.degree. C. for 18 h with technical grade manganese dioxide.

Claims Text - CLTX:

(a) transforming a microorganism with genetic elements comprising **pps and tkt genes** wherein said genes are expressed when said microorganism is grown in minimal medium containing glucose;

Claims Text - CLTX:

(b) overexpressing the **pps and tkt genes** in said microorganisms incubated in minimal medium containing glucose; and

Claims Text - CLTX:

3. The method of claim 1 wherein the **pps gene** is operably linked to a tac promoter.

Claims Text - CLTX:

(a) transforming a microorganism with genetic elements comprising **pps, tkt, and serA genes** wherein said genes are expressed when said microorganism is grown in a minimal medium containing glucose;

Claims Text - CLTX:

(b) overexpressing the **pps, tkt, and serA genes** in said microorganisms incubated in the media minimal medium containing glucose; and

Claims Text - CLTX:

10. The method of claim 8 wherein the **pps gene** is operably linked to a tac promoter.

Claims Text - CLTX:

(a) transforming a microorganism with genetic elements comprising **pps, tkt, and pheA.sup.fbr genes** wherein said genes are expressed when said microorganism is grown in minimal medium containing glucose;

Claims Text - CLTX:

17. The method of claim 15 wherein the **pps gene** is operably linked to a tac promoter.

Claims Text - CLTX:

(a) transforming a microorganism with genetic elements comprising **pps, tkt, and qad genes** wherein said genes are expressed when said microorganism is grown in minimal medium containing glucose;

Claims Text - CLTX:

(b) overexpressing the **pps, tkt, and qad genes** in said microorganisms incubated in minimal medium containing glucose; and

Claims Text - CLTX:

24. The method of claim 22 wherein the **pps gene** is operably linked to a tac promoter.

US-PAT-NO: 5714323

DOCUMENT-IDENTIFIER: US 5714323 A

TITLE: Over expression of single-stranded molecules

DATE-ISSUED: February 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ohshima; Atushi	Kyoto-fu	N/A	N/A	JP
Inouye; Sumiko	Bridgewater	NJ	N/A	N/A
Inouye; Masayori	Bridgewater	NJ	N/A	N/A

APPL-NO: 08/ 318867

DATE FILED: May 4, 1995

PARENT-CASE:

This is a 371 application of PCT/US94/02169, filed on Mar. 1, 1994, which is a continuation-in-part of pending application Ser. No. 08/284,860, filed on Aug. 2, 1994, which is a Continuation in Part of 08/024,676, filed on Mar. 1, 1993, which is a Continuation in Part of 07/753,111, filed on Aug. 30, 1991, abandoned. Both of these patent applications (parent applications) are explicitly incorporated herein word for word as if each had been fully reproduced hereinafter.

PCT-DATA:
APPL-NO: PCT/US94/02169
DATE-FILED: March 1, 1994
PUB-NO: WO94/20639
PUB-DATE: Sep 15, 1994
371-DATE: May 4, 1995
102(E)-DATE: May 4, 1995

US-CL-CURRENT: 435/6; 435/91.2

ABSTRACT:

A method of synthesis of new and useful single-stranded DNAs which have a stem-loop configuration (ss-slDNA). The method is an in vivo or an in vitro synthesis. Replicating vehicles which produce these ss-slDNAs. The ss-slDNAs are described. Uses for these slDNAs are disclosed. They can be used for introducing random mutations, they lend themselves for replication by a variant of the PCR method. They can also be used for regulating gene function. Other uses are disclosed.

24 Claims, 32 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 27

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Detailed Description Text - DETX:

The slDNA prepared in Example 10-2 was labelled with [.gamma.-.sup.32 P]ATP by phosphorylation. Triple helix was formed by mixing radiolabeled slDNA and excess target DNA in a 0.15M NaCl/10 mM MgCl.sub.2 /5 mM tris-**acetate** (pH7.0) buffer, and then incubating overnight at 37.degree. C. Triple helix formation was detected by 12% polyacrylamide gel electrophoresis in 50 mM tris-borate/5 mM MgCl.sub.2 (pH8.3) buffer.

Detailed Description Text - DETX:

Saccharomyces cerevisiae YPH499 cells (Stratagene) were transformed by pYES2-8-106 or pYES2-9-106 by the LiAc procedure [see Journal of Bacteriology, 153, 163-168, (1983)]. These transformants were grown on 100 ml of YPD medium (1% yeast extract, 2% bacto-peptone, 2% dextrose) to an OD.sub.600 of approximately 1.5. The cells were harvested by centrifugation, and washed once with 10 ml of SCE solution (182 g/l Sorbitol, 29.4 g/l Na.sub.2 Citrate, 22.3 g/l Na.sub.2 EDTA). Next, the cells were suspended in solution I (SCE solution containing 0.1% .beta.-mercaptoethanol and 0.5 mg/ml Zymolyase 100T) and shaken gently at 37.degree. C. for 2 hours to generate spheroplasts. Next, 8 ml of solution II (0.2N NaOH, 1% SDS) were added and the suspensions were held on ice for 5 minutes. Next, 6 ml of solution III (60 ml of 5M K-**acetate,** 11.5 ml of glacial acetic acid, 28.5 ml of H.sub.2 O) were added, held on ice for an additional 5 minutes, and then centrifuged. The DNAs were precipitated by addition of isopropanol to the supernatants, washed with 70% ethanol, and resuspended in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH7.6). The DNAs were further purified by phenol/chloroform extraction, ethanol precipitation, and using Qiagen tip 5 (Qiagen Inc.). Finally, the purified DNAs were suspended in 20 .mu.l of TE buffer.

Detailed Description Text - DETX:

Palindromes have been defined to include inverted repetitious sequences in which almost the same (not necessarily the same) sequences run in opposite direction. Though some are short (3-10 bases in one direction), others are much longer, comprising hundreds of base pairs. Watson, Molecular Biology of the **Gene, 3rd Ed., pps**. 224-225.

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   * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

 FILE 'HOME' ENTERED AT 15:08:14 ON 29 OCT 2002

 => fil .bec
 COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                            ENTRY    SESSION
 FULL ESTIMATED COST                                         0.42       0.42

 FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 15:09:07 ON 29 OCT 2002
 ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

 11 FILES IN THE FILE LIST

 => s glnap?
 FILE 'MEDLINE'
 L1           52 GLNAP?

 FILE 'SCISEARCH'
 L2           34 GLNAP?

 FILE 'LIFESCI'
 L3           47 GLNAP?

 FILE 'BIOTECHDS'
 L4            5 GLNAP?

 FILE 'BIOSIS'
 L5           55 GLNAP?

 FILE 'EMBASE'
 L6           44 GLNAP?

 FILE 'HCAPLUS'
 L7           60 GLNAP?

 FILE 'NTIS'
 L8            0 GLNAP?

 FILE 'ESBIOBASE'
 L9           21 GLNAP?

 FILE 'BIOTECHNO'
 L10          42 GLNAP?

 FILE 'WPIDS'
 L11           2 GLNAP?

 TOTAL FOR ALL FILES
 L12         362 GLNAP?

 => s acetyl phosphate or acetylphosphate or acetate
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          35790 ACETYL
         119651 PHOSPHATE
            316 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             70 ACETYLPHOSPHATE
          81903 ACETATE
 L13      82193 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

 FILE 'SCISEARCH'
          34943 ACETYL
```

```
         121121 PHOSPHATE
            296 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             29 ACETYLPHOSPHATE
          79836 ACETATE
L14       80096 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'LIFESCI'
          10238 "ACETYL"
          35241 "PHOSPHATE"
            158 ACETYL PHOSPHATE
                  ("ACETYL"(W)"PHOSPHATE")
             21 ACETYLPHOSPHATE
          22416 ACETATE
L15       22546 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'BIOTECHDS'
           2403 ACETYL
          14303 PHOSPHATE
             46 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             10 ACETYLPHOSPHATE
          10578 ACETATE
L16       10601 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'BIOSIS'
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         181622 PHOSPHATE
            413 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             74 ACETYLPHOSPHATE
         109899 ACETATE
L17      110254 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'EMBASE'
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         146726 "PHOSPHATE"
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                  ("ACETYL"(W)"PHOSPHATE")
             37 ACETYLPHOSPHATE
          96889 ACETATE
L18       97114 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'HCAPLUS'
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         463848 PHOSPHATE
            877 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
            229 ACETYLPHOSPHATE
         421366 ACETATE
L19      422115 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'NTIS'
            722 ACETYL
           6249 PHOSPHATE
              1 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
              1 ACETYLPHOSPHATE
           3034 ACETATE
L20        3034 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'ESBIOBASE'
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          32697 PHOSPHATE
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                  (ACETYL(W)PHOSPHATE)
             13 ACETYLPHOSPHATE
          20513 ACETATE
L21       20632 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'BIOTECHNO'
          11314 ACETYL
          46683 PHOSPHATE
            177 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             25 ACETYLPHOSPHATE
          27352 ACETATE
L22       27509 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

FILE 'WPIDS'
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          76736 PHOSPHATE
             30 ACETYL PHOSPHATE
                  (ACETYL(W)PHOSPHATE)
             17 ACETYLPHOSPHATE
         106135 ACETATE
L23      106160 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

TOTAL FOR ALL FILES
L24      982254 ACETYL PHOSPHATE OR ACETYLPHOSPHATE OR ACETATE

=> s promoter?
FILE 'MEDLINE'
L25       93024 PROMOTER?

FILE 'SCISEARCH'
L26       95214 PROMOTER?

FILE 'LIFESCI'
L27       55146 PROMOTER?

FILE 'BIOTECHDS'
L28       24138 PROMOTER?

FILE 'BIOSIS'
L29      104479 PROMOTER?

FILE 'EMBASE'
L30       77347 PROMOTER?

FILE 'HCAPLUS'
L31      144292 PROMOTER?

FILE 'NTIS'
L32        1416 PROMOTER?

FILE 'ESBIOBASE'
L33       47995 PROMOTER?

FILE 'BIOTECHNO'
L34       67372 PROMOTER?

FILE 'WPIDS'
L35       25952 PROMOTER?

TOTAL FOR ALL FILES
L36      736375 PROMOTER?
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=> s l12 and (l24 or l36(8a)(induc? or regulat? or activat? or modulat?))
FILE 'MEDLINE'
       1346107 INDUC?
        580948 REGULAT?
        537223 ACTIVAT?
        166473 MODULAT?
         27145 L25(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L37         32 L1 AND (L13 OR L25(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'SCISEARCH'
       1214321 INDUC?
        498967 REGULAT?
        622855 ACTIVAT?
        239169 MODULAT?
         25559 L26(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L38         23 L2 AND (L14 OR L26(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'LIFESCI'
        350123 INDUC?
        204346 REGULAT?
        186911 ACTIVAT?
         62472 MODULAT?
         18003 L27(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L39         29 L3 AND (L15 OR L27(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'BIOTECHDS'
         30817 INDUC?
         18650 REGULAT?
         18334 ACTIVAT?
          6054 MODULAT?
          4386 L28(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L40          4 L4 AND (L16 OR L28(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'BIOSIS'
       1261483 INDUC?
        640372 REGULAT?
        600401 ACTIVAT?
        196115 MODULAT?
         31109 L29(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L41         36 L5 AND (L17 OR L29(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'EMBASE'
       1030248 INDUC?
        480336 REGULAT?
        506874 ACTIVAT?
        160234 MODULAT?
         23647 L30(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L42         28 L6 AND (L18 OR L30(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'HCAPLUS'
       1675775 INDUC?
        726042 REGULAT?
       1010878 ACTIVAT?
        250128 MODULAT?
         39226 L31(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L43         43 L7 AND (L19 OR L31(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))
```

```
FILE 'NTIS'
         66157 INDUC?
         79496 REGULAT?
         27108 ACTIVAT?
         20723 MODULAT?
           226 L32(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L44          0 L8 AND (L20 OR L32(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'ESBIOBASE'
        363848 INDUC?
        265484 REGULAT?
        215718 ACTIVAT?
         74371 MODULAT?
         16473 L33(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L45         15 L9 AND (L21 OR L33(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT
               ?))

FILE 'BIOTECHNO'
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        205376 ACTIVAT?
         50925 MODULAT?
         21314 L34(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L46         26 L10 AND (L22 OR L34(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULA
               T?))

FILE 'WPIDS'
        208302 INDUC?
        323087 REGULAT?
        209112 ACTIVAT?
        129713 MODULAT?
          3285 L35(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)
L47          2 L11 AND (L23 OR L35(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULA
               T?))

TOTAL FOR ALL FILES
L48        238 L12 AND (L24 OR L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULA
               T?))

=> s l24(8a)l36(8a)(induc? or regulat? or activat? or modulat?)
FILE 'MEDLINE'
       1346107 INDUC?
        580948 REGULAT?
        537223 ACTIVAT?
        166473 MODULAT?
L49        620 L13(8A)L25(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'SCISEARCH'
       1214321 INDUC?
        498967 REGULAT?
        622855 ACTIVAT?
        239169 MODULAT?
L50        356 L14(8A)L26(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'LIFESCI'
        350123 INDUC?
        204346 REGULAT?
        186911 ACTIVAT?
         62472 MODULAT?
L51        232 L15(8A)L27(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'BIOTECHDS'
         30817 INDUC?
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```
          18650 REGULAT?
          18334 ACTIVAT?
           6054 MODULAT?
L52           6 L16(8A)L28(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'BIOSIS'
        1261483 INDUC?
         640372 REGULAT?
         600401 ACTIVAT?
         196115 MODULAT?
L53         680 L17(8A)L29(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'EMBASE'
        1030248 INDUC?
         480336 REGULAT?
         506874 ACTIVAT?
         160234 MODULAT?
L54         564 L18(8A)L30(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'HCAPLUS'
        1675775 INDUC?
         726042 REGULAT?
        1010878 ACTIVAT?
         250128 MODULAT?
L55         561 L19(8A)L31(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'NTIS'
          66157 INDUC?
          79496 REGULAT?
          27108 ACTIVAT?
          20723 MODULAT?
L56           3 L20(8A)L32(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'ESBIOBASE'
         363848 INDUC?
         265484 REGULAT?
         215718 ACTIVAT?
          74371 MODULAT?
L57         177 L21(8A)L33(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

FILE 'BIOTECHNO'
         299922 INDUC?
         236394 REGULAT?
         205376 ACTIVAT?
          50925 MODULAT?
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FILE 'WPIDS'
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         323087 REGULAT?
         209112 ACTIVAT?
         129713 MODULAT?
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TOTAL FOR ALL FILES
L60        3541 L24(8A) L36(8A)(INDUC? OR REGULAT? OR ACTIVAT? OR MODULAT?)

=> s l60 not ((phorbol or tetradecanoylphorbol)(2a)acetate)
FILE 'MEDLINE'
          30359 PHORBOL
          26228 TETRADECANOYLPHORBOL
          81903 ACETATE
          29838 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L61          41 L49 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)
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FILE 'SCISEARCH'
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         79836 ACETATE
         10874 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L62         81 L50 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'LIFESCI'
         11150 PHORBOL
          2247 TETRADECANOYLPHORBOL
         22416 ACETATE
          5480 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L63         48 L51 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'BIOTECHDS'
           247 PHORBOL
            41 TETRADECANOYLPHORBOL
         10578 ACETATE
           138 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L64          2 L52 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'BIOSIS'
         36736 PHORBOL
          9198 TETRADECANOYLPHORBOL
        109899 ACETATE
         21004 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L65        110 L53 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'EMBASE'
         36034 PHORBOL
          5894 TETRADECANOYLPHORBOL
         96889 ACETATE
         24345 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L66         43 L54 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'HCAPLUS'
         30263 PHORBOL
          6198 TETRADECANOYLPHORBOL
        421366 ACETATE
         15459 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L67        128 L55 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'NTIS'
           194 PHORBOL
            29 TETRADECANOYLPHORBOL
          3034 ACETATE
            80 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L68          0 L56 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'ESBIOBASE'
         10466 PHORBOL
          1883 TETRADECANOYLPHORBOL
         20513 ACETATE
          4365 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L69         52 L57 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

FILE 'BIOTECHNO'
         17739 PHORBOL
          3117 TETRADECANOYLPHORBOL
         27352 ACETATE
         11741 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L70         35 L58 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)
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FILE 'WPIDS'
           261 PHORBOL
            36 TETRADECANOYLPHORBOL
        106135 ACETATE
           121 (PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE
L71          4 L59 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A)ACETATE)

TOTAL FOR ALL FILES
L72        544 L60 NOT ((PHORBOL OR TETRADECANOYLPHORBOL)(2A) ACETATE)

=> s pps or phosphoenol pyruvate synthase#
FILE 'MEDLINE'
          2000 PPS
           221 PHOSPHOENOL
         22906 PYRUVATE
         65771 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L73       2000 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'SCISEARCH'
          1842 PPS
           214 PHOSPHOENOL
         17643 PYRUVATE
         74525 SYNTHASE#
             1 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L74       1843 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'LIFESCI'
           307 PPS
           112 "PHOSPHOENOL"
          5587 "PYRUVATE"
         18669 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 ("PHOSPHOENOL"(W)"PYRUVATE"(W)SYNTHASE#)
L75        307 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'BIOTECHDS'
            75 PPS
            70 PHOSPHOENOL
          1603 PYRUVATE
          3940 SYNTHASE#
             2 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L76         76 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'BIOSIS'
          1045 PPS
          3640 PHOSPHOENOL
         34091 PYRUVATE
         73871 SYNTHASE#
            10 PHOSPHOENOL PYRUVATE SYNTHASE#
                 (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
L77       1053 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

FILE 'EMBASE'
          1306 PPS
           172 "PHOSPHOENOL"
         18761 "PYRUVATE"
         65108 SYNTHASE#
             0 PHOSPHOENOL PYRUVATE SYNTHASE#
                 ("PHOSPHOENOL"(W)"PYRUVATE"(W)SYNTHASE#)
L78       1306 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#
```

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 FILE 'HCAPLUS'
           2472 PPS
            655 PHOSPHOENOL
          45729 PYRUVATE
          67744 SYNTHASE#
              5 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
 L79       2476 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

 FILE 'NTIS'
            681 PPS
              5 PHOSPHOENOL
            304 PYRUVATE
            194 SYNTHASE#
              0 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
 L80        681 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

 FILE 'ESBIOBASE'
            384 PPS
             68 PHOSPHOENOL
           5030 PYRUVATE
          28990 SYNTHASE#
              0 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
 L81        384 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

 FILE 'BIOTECHNO'
            216 PPS
             72 PHOSPHOENOL
           6022 PYRUVATE
          25465 SYNTHASE#
              0 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
 L82        216 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

 FILE 'WPIDS'
           1204 PPS
            139 PHOSPHOENOL
           1477 PYRUVATE
           2785 SYNTHASE#
              7 PHOSPHOENOL PYRUVATE SYNTHASE#
                (PHOSPHOENOL(W)PYRUVATE(W)SYNTHASE#)
 L83       1206 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

 TOTAL FOR ALL FILES
 L84      11548 PPS OR PHOSPHOENOL PYRUVATE SYNTHASE#

 => s l84(5a)gene/q
 FILE 'MEDLINE'
 L85          41 L73(5A)GENE/Q

 FILE 'SCISEARCH'
 L86          36 L74(5A)GENE/Q

 FILE 'LIFESCI'
 L87          26 L75(5A)GENE/Q

 FILE 'BIOTECHDS'
 L88          17 L76(5A)GENE/Q

 FILE 'BIOSIS'
 L89          49 L77(5A)GENE/Q
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FILE 'EMBASE'
L90          32 L78(5A)GENE/Q

FILE 'HCAPLUS'
L91          75 L79(5A)GENE/Q

FILE 'NTIS'
L92           1 L80(5A)GENE/Q

FILE 'ESBIOBASE'
L93          24 L81(5A)GENE/Q

FILE 'BIOTECHNO'
L94          27 L82(5A)GENE/Q

FILE 'WPIDS'
L95          25 L83(5A)GENE/Q

TOTAL FOR ALL FILES
L96         353 L84(5A) GENE/Q

=> s phosphoenolpyruvate synthase#
FILE 'MEDLINE'
          6144 PHOSPHOENOLPYRUVATE
         65771 SYNTHASE#
L97         25 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'SCISEARCH'
          5605 PHOSPHOENOLPYRUVATE
         74525 SYNTHASE#
L98         24 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'LIFESCI'
          2043 "PHOSPHOENOLPYRUVATE"
         18669 SYNTHASE#
L99         14 PHOSPHOENOLPYRUVATE SYNTHASE#
                 ("PHOSPHOENOLPYRUVATE"(W)SYNTHASE#)

FILE 'BIOTECHDS'
           372 PHOSPHOENOLPYRUVATE
          3940 SYNTHASE#
L100         9 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'BIOSIS'
          7441 PHOSPHOENOLPYRUVATE
         73871 SYNTHASE#
L101        42 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'EMBASE'
          4133 "PHOSPHOENOLPYRUVATE"
         65108 SYNTHASE#
L102        23 PHOSPHOENOLPYRUVATE SYNTHASE#
                 ("PHOSPHOENOLPYRUVATE"(W)SYNTHASE#)

FILE 'HCAPLUS'
         10418 PHOSPHOENOLPYRUVATE
         67744 SYNTHASE#
L103        72 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)
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FILE 'NTIS'
            37 PHOSPHOENOLPYRUVATE
           194 SYNTHASE#
L104         1 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'ESBIOBASE'
          1673 PHOSPHOENOLPYRUVATE
         28990 SYNTHASE#
L105        13 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'BIOTECHNO'
          2317 PHOSPHOENOLPYRUVATE
         25465 SYNTHASE#
L106        20 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

FILE 'WPIDS'
           169 PHOSPHOENOLPYRUVATE
          2785 SYNTHASE#
L107         5 PHOSPHOENOLPYRUVATE SYNTHASE#
                 (PHOSPHOENOLPYRUVATE(W)SYNTHASE#)

TOTAL FOR ALL FILES
L108       248 PHOSPHOENOLPYRUVATE SYNTHASE#

=> s l108(5a)gene/q
FILE 'MEDLINE'
L109         4 L97 (5A)GENE/Q

FILE 'SCISEARCH'
L110         5 L98 (5A)GENE/Q

FILE 'LIFESCI'
L111         3 L99 (5A)GENE/Q

FILE 'BIOTECHDS'
L112         4 L100(5A)GENE/Q

FILE 'BIOSIS'
L113        12 L101(5A)GENE/Q

FILE 'EMBASE'
L114         5 L102(5A)GENE/Q

FILE 'HCAPLUS'
L115        17 L103(5A)GENE/Q

FILE 'NTIS'
L116         0 L104(5A)GENE/Q

FILE 'ESBIOBASE'
L117         5 L105(5A)GENE/Q

FILE 'BIOTECHNO'
L118         5 L106(5A)GENE/Q

FILE 'WPIDS'
L119         2 L107(5A)GENE/Q

TOTAL FOR ALL FILES
L120        62 L108(5A) GENE/Q
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```
=> s (196 or l120) and l24
FILE 'MEDLINE'
L121          2 (L85 OR L109) AND L13

FILE 'SCISEARCH'
L122          2 (L86 OR L110) AND L14

FILE 'LIFESCI'
L123          1 (L87 OR L111) AND L15

FILE 'BIOTECHDS'
L124          0 (L88 OR L112) AND L16

FILE 'BIOSIS'
L125          3 (L89 OR L113) AND L17

FILE 'EMBASE'
L126          2 (L90 OR L114) AND L18

FILE 'HCAPLUS'
L127          5 (L91 OR L115) AND L19

FILE 'NTIS'
L128          0 (L92 OR L116) AND L20

FILE 'ESBIOBASE'
L129          0 (L93 OR L117) AND L21

FILE 'BIOTECHNO'
L130          2 (L94 OR L118) AND L22

FILE 'WPIDS'
L131          1 (L95 OR L119) AND L23

TOTAL FOR ALL FILES
L132         18 (L96 OR L120) AND L24

=> s (196 or l120)(5a)(overexpress? or amplif? or increas?)
FILE 'MEDLINE'
         41802 OVEREXPRESS?
         75666 AMPLIF?
       1643024 INCREAS?
L133          0 (L85 OR L109)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'SCISEARCH'
         47978 OVEREXPRESS?
        119690 AMPLIF?
       1581049 INCREAS?
L134          0 (L86 OR L110)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'LIFESCI'
         19071 OVEREXPRESS?
         37654 AMPLIF?
        428744 INCREAS?
L135          0 (L87 OR L111)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'BIOTECHDS'
          2346 OVEREXPRESS?
         18407 AMPLIF?
         49994 INCREAS?
L136          1 (L88 OR L112)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'BIOSIS'
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          47316 OVEREXPRESS?
         106170 AMPLIF?
        1821322 INCREAS?
L137          2 (L89 OR L113)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'EMBASE'
          39882 OVEREXPRESS?
          68623 AMPLIF?
        1576754 INCREAS?
L138          0 (L90 OR L114)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'HCAPLUS'
          42506 OVEREXPRESS?
         130280 AMPLIF?
        3393229 INCREAS?
L139          5 (L91 OR L115)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'NTIS'
            537 OVEREXPRESS?
          17471 AMPLIF?
         175029 INCREAS?
L140          0 (L92 OR L116)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'ESBIOBASE'
          30338 OVEREXPRESS?
          38265 AMPLIF?
         516386 INCREAS?
L141          0 (L93 OR L117)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'BIOTECHNO'
          30184 OVEREXPRESS?
          60208 AMPLIF?
         342717 INCREAS?
L142          0 (L94 OR L118)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

FILE 'WPIDS'
           1399 OVEREXPRESS?
         220280 AMPLIF?
        1055931 INCREAS?
L143          0 (L95 OR L119)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

TOTAL FOR ALL FILES
L144          8 (L96 OR L120)(5A)(OVEREXPRESS? OR AMPLIF? OR INCREAS?)

=> s (l48 or l72 or l132 or l144) not 2001-2002/py
FILE 'MEDLINE'
         899423 2001-2002/PY
L145         67 (L37 OR L61 OR L121 OR L133) NOT 2001-2002/PY

FILE 'SCISEARCH'
        1666861 2001-2002/PY
L146         89 (L38 OR L62 OR L122 OR L134) NOT 2001-2002/PY

FILE 'LIFESCI'
         148948 2001-2002/PY
L147         70 (L39 OR L63 OR L123 OR L135) NOT 2001-2002/PY

FILE 'BIOTECHDS'
          26198 2001-2002/PY
L148          4 (L40 OR L64 OR L124 OR L136) NOT 2001-2002/PY

FILE 'BIOSIS'
         858487 2001-2002/PY
L149        134 (L41 OR L65 OR L125 OR L137) NOT 2001-2002/PY
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FILE 'EMBASE'
        738481 2001-2002/PY
L150         67 (L42 OR L66 OR L126 OR L138) NOT 2001-2002/PY

FILE 'HCAPLUS'
       1762327 2001-2002/PY
L151        154 (L43 OR L67 OR L127 OR L139) NOT 2001-2002/PY

FILE 'NTIS'
         22183 2001-2002/PY
L152          0 (L44 OR L68 OR L128 OR L140) NOT 2001-2002/PY

FILE 'ESBIOBASE'
        482916 2001-2002/PY
L153         54 (L45 OR L69 OR L129 OR L141) NOT 2001-2002/PY

FILE 'BIOTECHNO'
        201150 2001-2002/PY
L154         57 (L46 OR L70 OR L130 OR L142) NOT 2001-2002/PY

FILE 'WPIDS'
       1630167 2001-2002/PY
L155          2 (L47 OR L71 OR L131 OR L143) NOT 2001-2002/PY

TOTAL FOR ALL FILES
L156        698 (L48 OR L72 OR L132 OR L144) NOT 2001-2002/PY

=> dup rem l156
PROCESSING COMPLETED FOR L156
L157         225 DUP REM L156 (473 DUPLICATES REMOVED)

=> d tot

L157 ANSWER 1 OF 225  HCAPLUS  COPYRIGHT 2002 ACS
TI   L-Amino acid biosynthesis in genetically engineered coryneform bacteria
     with enhanced phosphoenolpyruvate synthase activity
SO   PCT Int. Appl., 24 pp.
     CODEN: PIXXD2
IN   Sugimoto, Masakazu; Ito, Hisao; Kurahashi, Osamu
AN   2000:688344  HCAPLUS
DN   133:265707
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   WO 2000056859     A1    20000928       WO 2000-JP1655   20000317
         W:  AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE,
             GD, GE, HR, HU, ID, IL, IN, IS, JP, KR, LC, LK, LR, LT, LV, MA,
             MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ,
             VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
             DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

L157 ANSWER 2 OF 225     MEDLINE                              DUPLICATE 1
TI   Superoxide production and reactive oxygen species signaling by endothelial
     nitric-oxide synthase.
SO   JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jun 2) 275 (22) 16899-903.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Wang W; Wang S; Yan L; Madara P; Del Pilar Cintron A; Wesley R A; Danner R
     L
AN   2000287564     MEDLINE

L157 ANSWER 3 OF 225  SCISEARCH  COPYRIGHT 2002 ISI (R) DUPLICATE 2
TI   Raf induces NF-kappa B by membrane shuttle kinase MEKK1, a signaling
```

pathway critical for transformation
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (25 APR 2000) Vol. 97, No. 9, pp. 4615-4620.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
ISSN: 0027-8424.
AU Baumann B; Weber C K; Troppmair J; Whiteside S; Israel A; Rapp U R; Wirth T (Reprint)
AN 2000:340920 SCISEARCH

L157 ANSWER 4 OF 225 MEDLINE DUPLICATE 3
TI Simultaneous binding of two DNA duplexes to the NtrC-enhancer complex studied by two-color fluorescence cross-correlation spectroscopy.
SO BIOCHEMISTRY, (2000 Mar 7) 39 (9) 2131-9.
Journal code: 0370623. ISSN: 0006-2960.
AU Rippe K
AN 2000160489 MEDLINE

L157 ANSWER 5 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Matrix metalloproteinase 9 promoter activity is induced coincident with invasion during tumor progression
SO American Journal of Pathology (2000), 157(6), 1777-1783
CODEN: AJPAA4; ISSN: 0002-9440
AU Kupferman, Michael E.; Fini, M. Elizabeth; Muller, William J.; Weber, Randal; Cheng, Yi; Muschel, Ruth J.
AN 2001:14676 HCAPLUS
DN 134:324366

L157 ANSWER 6 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Structure-Activity Relationships of (1'S)-1'-Acetoxychavicol Acetate, a Major Constituent of a Southeast Asian Condiment Plant Languas galanga, on the Inhibition of Tumor-Promoter-Induced Epstein-Barr Virus Activation
SO Journal of Agricultural and Food Chemistry (2000), 48(5), 1518-1523
CODEN: JAFCAU; ISSN: 0021-8561
AU Murakami, Akira; Toyota, Kazuo; Ohura, Shin; Koshimizu, Koichi; Ohigashi, Hajime
AN 2000:238648 HCAPLUS
DN 133:37710

L157 ANSWER 7 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Mucosa-specific targets for regulation of IFN-.gamma. expression: lamina propria T cells use different cis-elements than peripheral blood T cells to regulate transactivation of IFN-.gamma. expression
SO Journal of Immunology (2000), 164(3), 1399-1407
CODEN: JOIMA3; ISSN: 0022-1767
AU Gonsky, Rivkah; Deem, Richard L.; Bream, Jay H.; Lee, Doo Han; Young, Howard A.; Targan, Stephan R.
AN 2000:82590 HCAPLUS
DN 132:221193

L157 ANSWER 8 OF 225 MEDLINE DUPLICATE 4
TI Activation of osteocalcin transcription involves interaction of protein kinase A- and protein kinase C-dependent pathways.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Jan 14) 275 (2) 999-1006.
Journal code: 2985121R. ISSN: 0021-9258.
AU Boguslawski G; Hale L V; Yu X P; Miles R R; Onyia J E; Santerre R F; Chandrasekhar S
AN 2000092866 MEDLINE

L157 ANSWER 9 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Allele-specific regulation of matrix metalloproteinase-12 gene activity is associated with coronary artery luminal dimensions in diabetic patients with manifest coronary artery disease
SO Circulation Research (2000), 86(9), 998-1003

CODEN: CIRUAL; ISSN: 0009-7330
AU Jormsjo, Sofia; Ye, Shu; Moritz, Joseffa; Walter, Dirk H.; Dimmeler, Stefanie; Zeiher, Andreas M.; Henney, Adriano; Hamsten, Anders; Eriksson, Per
AN 2000:346530 HCAPLUS
DN 133:87647

L157 ANSWER 10 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI Molecular regulation of granulocyte macrophage colony-stimulating factor in human lung epithelial cells by interleukin (IL)-1beta, IL-4, and IL-13 involves both transcriptional and post-transcriptional mechanisms.
SO American Journal of Respiratory Cell and Molecular Biology, (May, 2000) Vol. 22, No. 5, pp. 582-589. print.
ISSN: 1044-1549.
AU Bergmann, Martin; Barnes, Peter J.; Newton, Robert (1)
AN 2000:321497 BIOSIS

L157 ANSWER 11 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Improving lycopene production in Escherichia coli by engineering metabolic control
SO Nature Biotechnology (2000), 18(5), 533-537
CODEN: NABIF9; ISSN: 1087-0156
AU Farmer, William R.; Liao, James C.
AN 2000:346026 HCAPLUS
DN 133:88250

L157 ANSWER 12 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)DUPLICATE 5
TI The effect of PKC activation on the survival of rat retinal ganglion cells in culture
SO BRAIN RESEARCH, (24 JAN 2000) Vol. 853, No. 2, pp. 338-343.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0006-8993.
AU dosSantos A A; deAraujo E G (Reprint)
AN 2000:124969 SCISEARCH

L157 ANSWER 13 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI The transcriptional mechanisms of retinoid-induced tissue factor suppression in leukemic cell lines.
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 257a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
AU Tenno, Taavo (1); Oberg, Fredrik; Nilsson, Kenneth; Siegbahn, Agneta (1)
AN 2001:311579 BIOSIS

L157 ANSWER 14 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI PKC and ERK1/2 regulate amylase promoter activity during differentiation of a salivary gland cell line
SO Journal of Cellular Physiology (2000), 185(2), 215-225
CODEN: JCLLAX; ISSN: 0021-9541
AU Jung, Dale W.; Hecht, Dalit; Ho, Susan W.; O'Connell, Brian C.; Kleinman, Hynda K.; Hoffman, Matthew P.
AN 2000:708325 HCAPLUS
DN 133:306006

L157 ANSWER 15 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)
TI Evaluation of antimutagenic effect of todralazine in cultured lymphocytes
SO MUTAGENESIS, (MAR 2000) Vol. 15, No. 2, pp. 137-141.
Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
ISSN: 0267-8357.
AU Gasiorowski K (Reprint); Brokos B
AN 2000:244231 SCISEARCH

L157 ANSWER 16 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 6
TI Phorbols: Chemical synthesis and chemical biology
SO YAKUGAKU ZASSHI-JOURNAL OF THE PHARMACEUTICAL SOCIETY OF JAPAN, (JAN 2000) Vol. 120, No. 1, pp. 76-90.
Publisher: PHARMACEUTICAL SOC JAPAN, 2-12-15-201 SHIBUYA, SHIBUYA-KU, TOKYO 150, JAPAN.
ISSN: 0031-6903.
AU Shibasaki M (Reprint)
AN 2000:36917 SCISEARCH

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E-mail: diannew@qimr.edu.au

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CODEN: CNREA8 ISSN: 0008-5472
DT Journal; Article
CY United States
LA English
SL English

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L157 ANSWER 54 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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	EP 733704	A3	19961023		
	EP 733704	B1	19971015		
	R: AT, BE, DE, DK, FR, GB, NL				
	DE 19514056	A1	19961017	DE 1995-19514056	19950413
	US 5830692	A	19981103	US 1996-614686	19960312
	CA 2171668	AA	19960925	CA 1996-2171668	19960313
	JP 08266291	A2	19961015	JP 1996-64602	19960321
	AT 159290	E	19971115	AT 1996-104475	19960321
	FI 9601323	A	19960925	FI 1996-1323	19960322

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AN 1996:346150 HCAPLUS
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	W: CA, MX, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2199853	AA	19960321	CA 1995-2199853	19950915
	EP 782621	A1	19970709	EP 1995-931835	19950915
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	US 5906925	A	19990525	US 1997-801454	19970218
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CODEN: FEREAC; ISSN: 0097-6326
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L157 ANSWER 73 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 84 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 89 OF 225 MEDLINE DUPLICATE 49
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L157 ANSWER 90 OF 225 MEDLINE DUPLICATE 50
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L157 ANSWER 95 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)DUPLICATE 54
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L157 ANSWER 98 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 99 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 102 OF 225 MEDLINE DUPLICATE 58
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L157 ANSWER 111 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 112 OF 225 MEDLINE DUPLICATE 64
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L157 ANSWER 113 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 65
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L157 ANSWER 114 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)
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L157 ANSWER 115 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 66
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L157 ANSWER 116 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 67
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L157 ANSWER 119 OF 225 MEDLINE DUPLICATE 70
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L157 ANSWER 120 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 123 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 124 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 125 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 128 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 131 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 133 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 134 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 146 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 148 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 150 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 153 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 157 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 162 OF 225 MEDLINE DUPLICATE 94
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L157 ANSWER 166 OF 225 MEDLINE DUPLICATE 96
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L157 ANSWER 172 OF 225 LIFESCI COPYRIGHT 2002 CSA DUPLICATE 100
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L157 ANSWER 174 OF 225 LIFESCI COPYRIGHT 2002 CSA DUPLICATE 101
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L157 ANSWER 175 OF 225 MEDLINE DUPLICATE 102
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L157 ANSWER 176 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 177 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 178 OF 225 LIFESCI COPYRIGHT 2002 CSA DUPLICATE 103
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 61271221	A2	19861201	JP 1985-113175	19850528

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L157 ANSWER 182 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 183 OF 225 HCAPLUS COPYRIGHT 2002 ACS

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L157 ANSWER 184 OF 225 MEDLINE DUPLICATE 107
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L157 ANSWER 185 OF 225 MEDLINE DUPLICATE 108
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SO CELL, (1986 Jun 20) 45 (6) 785-92.
Journal code: 0413066. ISSN: 0092-8674.
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L157 ANSWER 186 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 188 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)DUPLICATE 109
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L157 ANSWER 190 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 191 OF 225 MEDLINE DUPLICATE 112
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L157 ANSWER 192 OF 225 MEDLINE DUPLICATE 113
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AN 85166256 MEDLINE

L157 ANSWER 193 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 114
TI TUMOR **PROMOTER** PHORBOL-12-MYRISTATE-13-**ACETATE** **INDUCES** POLY(ADP)-RIBOSYLATION IN FIBROBLASTS
SO EMBO JOURNAL, (1985) Vol. 4, No. 6, pp. 1491-1494.
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AN 85:379140 SCISEARCH

L157 ANSWER 194 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 115
TI TUMOR **PROMOTER** PHORBOL-12-MYRISTATE-13-**ACETATE** **INDUCES** POLY ADP-RIBOSYLATION IN HUMAN-MONOCYTES
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1985) Vol. 126, No. 3, pp. 1208-1214.
AU SINGH N (Reprint); POIRIER G; CERUTTI P
AN 85:122332 SCISEARCH

L157 ANSWER 195 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 116
TI TUMOR **PROMOTER** PHORBOL 12-MYRISTATE, 13-**ACETATE** INHIBITS PHOSPHOINOSITIDE HYDROLYSIS AND CYTOSOLIC CA-2& RISE **INDUCED** BY THE ACTIVATION OF MUSCARINIC RECEPTORS IN PC12 CELLS
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1985) Vol. 127, No. 1, pp. 310-317.
AU VICENTINI L M (Reprint); DIVIRGILIO F; AMBROSINI A; POZZAN T; MELDOLESI J
AN 85:140931 SCISEARCH

L157 ANSWER 196 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI PHORBOL-12-MYRISTATE-13-ACETATE INDUCES ENDOCYTOSIS AS WELL AS EXOCYTOSIS AND HYDROOSMOSIS IN TOAD BUFO-MARINUS URINARY BLADDER.
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L157 ANSWER 197 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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DN 104:223994

L157 ANSWER 198 OF 225 HCAPLUS COPYRIGHT 2002 ACS

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CODEN: BGASEB
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L157 ANSWER 199 OF 225 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 117
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L157 ANSWER 200 OF 225 LIFESCI COPYRIGHT 2002 CSA DUPLICATE 118
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L157 ANSWER 201 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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L157 ANSWER 202 OF 225 MEDLINE DUPLICATE 119
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L157 ANSWER 203 OF 225 MEDLINE DUPLICATE 120
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L157 ANSWER 204 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 205 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 206 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 207 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)DUPLICATE 121
TI TUMOR **PROMOTER** PHORBOL-12-MYRISTATE-13-**ACETATE** (TPA) **INDUCING** THE PROTEIN IN HUMAN-LYMPHOCYTES WHICH BINDS SATELLITE DNA
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L157 ANSWER 208 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)
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L157 ANSWER 209 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)
TI SUPPRESSION OF TUMOR **PROMOTER** PHORBOLMYRISTATE **ACETATE** -**INDUCED** CHROMOSOME BREAKAGE BY ANTI-OXIDANT AND INHIBITORS OF ARACHIDONIC-ACID METABOLISM
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L157 ANSWER 210 OF 225 LIFESCI COPYRIGHT 2002 CSA DUPLICATE 122
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L157 ANSWER 211 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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DN 98:193098

L157 ANSWER 212 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)DUPLICATE 123
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L157 ANSWER 213 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE 124
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L157 ANSWER 214 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 215 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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CODEN: PRLIDS; ISSN: 0275-3618
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L157 ANSWER 216 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 217 OF 225 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 125
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CODEN: CNREA8
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L157 ANSWER 218 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. DUPLICATE 126
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L157 ANSWER 219 OF 225 SCISEARCH COPYRIGHT 2002 ISI (R)DUPLICATE 127
TI TUMOR **PROMOTER** PHORBOL-12-MYRISTATE-13-**ACETATE** **INDUCES** CHROMOSOMAL DAMAGE VIA INDIRECT ACTION
SO NATURE, (1981) Vol. 293, No. 5828, pp. 144-146.
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AN 81:409795 SCISEARCH

L157 ANSWER 220 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI PURIFICATION OF PLASMINOGEN ACTIVATOR FROM ROUS SARCOMA VIRUS TRANSFORMED CHICK EMBRYO FIBROBLASTS TREATED WITH THE TUMOR PROMOTER PHORBOL 12 MYRISTATE 13 ACETATE.
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L157 ANSWER 221 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 222 OF 225 HCAPLUS COPYRIGHT 2002 ACS
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CODEN: BEXXAL
IN Okai, Sakuo; Kimoto, Koichi
AN 1980:458254 HCAPLUS
DN 93:58254

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	NO 7902905	A	19800312	NO 1979-2905	19790907
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	NL 7906776	A	19800313	NL 1979-6776	19790911
	IN 152081	A	19831015	IN 1979-CA1002	19790924

L157 ANSWER 223 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
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L157 ANSWER 224 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Catalyst, containing zinc acetate and cadmium acetate applied on activated coal, for vapor-phase synthesis of complex vinyl esters from acetylene and carboxylic acids
SO U.S.S.R.
From: Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki 1976, 53(48), 20.
CODEN: URXXAF
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AN 1977:96656 HCAPLUS
DN 86:96656

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PI	SU 540658	T	19761230	SU 1975-2157670	19750603

L157 ANSWER 225 OF 225 HCAPLUS COPYRIGHT 2002 ACS
TI Salmonella locus affecting phosphoenolpyruvate synthase activity identified by a deletion analysis
SO J. Bacteriol. (1971), 106(1), 286-8
CODEN: JOBAAY
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AN 1971:121790 HCAPLUS
DN 74:121790

=> save temp l157 glnap2/a
ANSWER SET L157 HAS BEEN SAVED AS 'GLNAP2/A'

=> d ab
11,26,27,38,45,47,57,58,60,71,72,74,76,85,94,96,100,102,104,110-112,117,119,126-128,
131,138,141,145,146,150,154,161,163,170,174,181,191,192,203

L157 ANSWER 11 OF 225 HCAPLUS COPYRIGHT 2002 ACS
AB Metabolic engineering has achieved encouraging success in producing foreign metabolites in a variety of hosts. However, common strategies for engineering metabolic pathways focus on amplifying the desired enzymes and deregulating cellular controls. As a result, uncontrolled or deregulated metabolic pathways lead to metabolic imbalance and suboptimal productivity. The second stage of metabolic engineering effort was demonstrated by designing and engineering a regulatory circuit to control gene expression in response to intracellular metabolic states. Specifically, one of the global regulatory systems in Escherichia coli, the Ntr regulon, was recruited and altered to control the engineered lycopene biosynthesis pathway. The artificially engineered regulon, stimulated by excess glycolytic flux through sensing of an intracellular metabolite, **acetyl phosphate**, controls the expression of two key enzymes in lycopene synthesis in response to flux dynamics. This intracellular control loop significantly enhanced lycopene prodn. while reducing the neg. impact caused by metabolic imbalance. Although we demonstrated this strategy for metabolite prodn., it can be extended into other fields where gene expression must be closely controlled by intracellular physiol., such as gene therapy.

L157 ANSWER 26 OF 225 MEDLINE DUPLICATE 13
AB Regulation of transcription by the form of RNA polymerase that contains sigma(N) involves activation at a distance by activators bound to sites located far upstream of the transcription start site, which contact RNA polymerase bound to the promoter via formation of a DNA loop. At the g/nAp2 **promoter**, binding sites for the **activator** NtrC show features characteristic of eukaryotic enhancers. A multiple response element containing binding sites for five sigma(N)-dependent activators from different systems has been cloned in different positions relative to the **glnAp2 promoter**. These **promoter** regions indeed allowed **activation** in vivo by each **regulator**, thus showing that transcription from an eubacterial **promoter** may be controlled in a very versatile way by different signals. The activation capability of each activator has been assessed in relation to its concentration, and the presence and relative positions of the corresponding binding sites in the DNA. Results show that most activators can function from any position. However, activation mediated by DctD-L64 was very sensitive to changes in the position of its binding sites. Transcriptional activation by combinations of two regulators was also tested and no significant synergism or interference was detected. Mapping of the 5' ends of the transcripts showed that neither the activator nor the position from which they activate influences selection of the transcription start site.

L157 ANSWER 27 OF 225 MEDLINE DUPLICATE 14
AB The **inducible** glnA **promoter** 2 of the E. coli glutamine synthetase gene is suitable as an expression unit for the production of recombinant proteins at low and high cell densities. It is active when the concentration of ammonium as the sole nitrogen source in the culture medium is below 1 mM. This nitrogen regulatory system was optimized by introduction of expression cassettes consisting of additional elements of the ntr-system. These artificial constructions result in enhanced recombinant gene expression in the production phase. Furthermore, the basic recombinant protein level during the growth phase is reduced due to a tighter promoter control. A three- to four-fold higher accumulation of chloramphenicol-acetyltransferase (as reporter protein) and of

anti-EGF-receptor miniantibodies was achieved by increasing the amount of the final regulator molecule NtrC approximately P via plasmidal co-expression of the ntrC gene. The introduction of a modified glnA promoter 1 inverse to **glnAp2** lowered the basic activity of **glnAp2** to about one half. It is assumed that under nitrogen excess conditions sigma 70-RNA polymerase binds at **glnAp1** and thereby prevents most of the binding of sigma 54-RNA polymerase at **glnAp2** . The optimized expression systems were successfully applied in low and high cell density cultivations. In the fed-batch phase of high cell density cultivations recombinant protein formation was induced through external nitrogen limitation under FIA-controlled concentration of glucose as carbon source.

L157 ANSWER 38 OF 225 MEDLINE DUPLICATE 21

AB Analysis of the **promoter** region of the **acetate-induced** isocitrate lyase gene (acu-3) of Neurospora crassa was undertaken. A series of deletions in the 5' non-transcribed region were constructed and the effects of these mutations on the enzyme levels following growth on sucrose and transfer to acetate were measured. Sequences within the region -603 to -271 relative to the transcription start site appear essential for transcription. The region -950 to -1278 is required for sucrose repression, which is consistent with previous protein/DNA gel retardation results of protein extracts from N. crassa cultured on sucrose. Protein extracts from **acetate-induced** mycelia identify alternative **promoter** regions apparently involved in **acetate-induced** gene transcription.

L157 ANSWER 45 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB A topoisomer gel retardation assay has been used to examine the topol. requirements for the formation of open promoter complexes on DNA minicircles carrying .sigma.54-dependent promoters. In the absence of intercalators, individual topoisomers carrying both the nifL and nifF promoters could be resolved as discrete species by electrophoresis, but exhibited anomalous electrophoretic behavior at relatively high neg. superhelical d., indicative of a structural transition. In the presence of phosphorylated activator protein NTRC, ATP, and .sigma.54 RNA polymerase holoenzyme, discrete topoisomer shifts were detected assocd. with the formation of open promoter complexes. At the nifL promoter open complexes could be formed on all neg. supercoiled topoisomers examd. as well as on nicked circular DNA, but not on the .DELTA.Lk = 0 topoisomer or pos. supercoiled DNA. Minicircles carrying the .sigma.54-dependent **glnAp2** promoter could not be resolved in the electrophoresis system, but using a combination of potassium permanganate footprinting and topoisomerase I relaxation assays, we found in contrast to the nifL promoter, that open complexes were formed not only on neg. supercoiled topoisomers but also on relaxed minicircles and the .DELTA.Lk = +1 topoisomer. These results indicate there is a thermodn. barrier to the formation of open complexes on DNA minicircles carrying the nifL promoter which is not evident at **glnAp2**.

L157 ANSWER 47 OF 225 MEDLINE DUPLICATE 26

AB We have examined the effects on transcription initiation of promoter and enhancer strength and of the curvature of the DNA separating these entities on wild-type and mutated enhancer-promoter regions at the Escherichia coli sigma54-dependent promoters **glnAp2** and glnHp2 on supercoiled and linear DNA. Our results, together with previously reported observations by other investigators, show that the initiation of transcription on linear DNA requires a single intrinsic or **induced** bend in the DNA, as well as a **promoter** with high affinity for sigma54-RNA polymerase, but on supercoiled DNA requires either such a bend or a high affinity promoter but not both. The examination of the DNA sequence of all nif gene **activator**- or nitrogen **regulator** I-sigma54 **promoters** reveals that those lacking

a binding site for the integration host factor have an intrinsic single bend in the DNA separating enhancer from promoter.

L157 ANSWER 57 OF 225 HCAPLUS COPYRIGHT 2002 ACS DUPLICATE 32
AB A regulatory system that allows control gene expression in a microbial host using a combination of oxygen partial pressure, pH, and acetate concn. is described. The promoter is from the bud operon of Klebsiella terrigena and its regulation is controlled by the BudR gene product. A reporter gene system for Klebsiella terrigena using the promoter of the budA gene of the budABC operon was constructed and tested in a fermentor. In aerobic conditions, the induction of the gene increase slightly between pH 6.0 and 8.0 and acetate repressed expression. In anaerobic conditions, induction fell with pH and acetate was a strong inducer at pH 6.0 but was without effect at alk. pH's.

L157 ANSWER 58 OF 225 HCAPLUS COPYRIGHT 2002 ACS
AB A method of achieving overprodn. of 3-deoxy-D-arabino-heptulosonate 7-phosphate (DAHP) by increasing the size of the phosphoenol pyruvate pool by high-level expression of the pps gene encoding a phosphoenol pyruvate synthase is described. Expression vectors the **pps gene** are used to **increase** diversion of carbon resources into the common arom. pathway and pathways branching from it. Other genes involved in the biosynthesis of arom. compds. can also be incorporated into the transgenic microorganism. The overexpression of phosphoenol pyruvate synthase increases DAHP prodn. to near theor. yields.

L157 ANSWER 60 OF 225 MEDLINE DUPLICATE 33
AB In vitro transcription, DNase I footprinting, and abortive initiation assays were used to characterize transcription using mutant forms of sigma 54 shown previously to bypass certain enhancer requirements in vitro. The holoenzymes containing these sigma mutants produce low levels of open complexes at both the **glnAp2** and glnHp2 promoters. The open complexes are unusual in that they are destroyed by heparin. Enhancer protein and ATP convert them into a stable heparin-resistant state. The enhancer response occurs over a similar range of NtrC concentration as occurs with the wild-type holoenzyme, indicating that the activation determinants have been largely preserved within these mutants. One-round transcription assays show that the mutant holoenzymes can be driven to transcribe both **promoters** without NtrC. The unstable opening **induced** by these mutations apparently serves as a conduit that can shuttle templates into transcriptionally competent complexes. The results lead to a model in which activation occurs in two steps. First, the enhancer complex overcomes an inhibitory effect of the sigma 54 leucine patch and unlocks the melting activity of the holoenzyme. Second, different sigma 54 determinants are used to drive stabilization of the open complexes, allowing the full transcription potential to be realized.

L157 ANSWER 71 OF 225 MEDLINE DUPLICATE 38
AB The **promoter** regions of four **acetate-inducible** genes of Neurospora crassa, acu-3, acu-5, acu-8 and acu-9, have been sequenced. Using a scanning gel mobility shift assay particular DNA regions in each promoter have been shown specifically to bind partially purified protein extracted from acetate-induced mycelia. The protein-binding regions so defined have common sequence motifs, elements of which are similar to those required for acetate induction in aspergillus nidulans.

L157 ANSWER 72 OF 225 MEDLINE DUPLICATE 39
AB The initiation of transcription (open complex formation) on supercoiled DNA templates carrying the sigma 54-dependent **promoters** **glnAp2** or glnHp2 can be readily **activated** by NR1-phosphate bound to sites located 100 bp upstream from the transcriptional start site. In the case of **glnAp2**, open complex formation can also be activated by NR1-phosphate on a linear template, but

in the case of glnHp2 activation on a linear template requires in addition to NR1-phosphate, a DNA-bending protein such as the histone-like protein HU or integration host factor (IHF). Moving the binding sites for NR1 200 bp further away from glnHp2 allows transcription to be activated equally well in the absence or presence of HU, and in this case IHF inhibits the open complex formation. Furthermore, replacement of the DNA segment separating the binding sites for NR1 from **glnAp2** by a random sequence of bases of equal length, does not reduce open complex formation on supercoiled DNA but prevents open complex formation on linear DNA unless HU is provided. These observations indicate that with binding sites for NR1 located in their usual position, 100 bp from the transcriptional start site, the DNA segment separating these sites from the promoter must be either intrinsically bent or bent by HU or, in the case of glnHp2, by IHF to allow contact between **activator** and the sigma 54-RNA polymerase-**promoter** complex. Computer simulation of the shape of the DNA suggests that in the case of **glnAp2**, but not of glnHp2 or the altered **glnAp2**, this segment has an intrinsic curvature of 70 degrees.

L157 ANSWER 74 OF 225 MEDLINE DUPLICATE 40

AB The use of a modified Escherichia coli **glnAP2** promoter results in the formation of both homologous and heterologous, cytoplasmic and periplasmic recombinant proteins in a nitrogen concentration dependent manner. As in the E. coli nitrogen regulatory system, **glnAP2** controlled gene expression is induced when ammonium concentration in the growth medium is below 1 mM (nitrogen limitation), otherwise only extremely low expression of recombinant genes is observed. Both high cell density cultivations (HCDC) and low cell density cultivations (LCDC) gave similar results for inducibility and formation of the following recombinant proteins: chloramphenicol-acetyltransferase, phosphorylcholine binding mini-antibodies (scFv-dhlx of McPC603) and K1-streptokinase. Recombinant proteins were formed in quantities of about 2-3% of total cellular protein. At low cell densities, slightly higher quantities resulted under partial nitrogen limitations than under total nitrogen limitation. In contrast, high cell density cultivations resulted in lower product concentrations at partial nitrogen limitation compared with total nitrogen limitation. These lowered product concentrations were probably due to the very high amounts of K+ or Na+ ions which accumulated during pH-regulation, thereby disturbing growth. HCDC under partial nitrogen limitation decreased proteolysis of recombinant proteins, therefore reduced amounts of proteases are considered to be responsible.

L157 ANSWER 76 OF 225 MEDLINE DUPLICATE 42

AB The nac gene of Klebsiella aerogenes encodes a bifunctional transcription factor that activates or represses the expression of several operons under conditions of nitrogen limitation. In experiments with purified components, transcription from the nac promoter was initiated by sigma 54 RNA polymerase and was activated by the phosphorylated form of nitrogen **regulator** I (NRI) (NtrC). The **activation** of the nac **promoter** required a higher concentration of NRI approximately P than did the **activation** of the Escherichia coli **glnAp2** **promoter**, and both the promoter and upstream enhancer element contributed to this difference. The nac promoter had a lower affinity for sigma 54 RNA polymerase than did **glnAp2**, and uninitiated competitor-resistant transcription complexes formed at the nac promoter decayed to competitor-sensitive complexes at a greater rate than did similar complexes formed at the **glnAp2** promoter. The nac enhancer, consisting of a single high-affinity NRI-binding site and an adjacent site with low affinity for NRI, was less efficient in stimulating transcription than was the glnA enhancer, which consists of two adjacent high-affinity NRI-binding sites. When these binding sites were exchanged, transcription from the nac promoter was increased and transcription from the **glnAp2** promoter was decreased at low concentrations of NRI approximately P. Another indication of the difference in the efficiency of

these enhancers is that although **activation** of a nac **promoter** construct containing the glnA enhancer was relatively insensitive to subtle alterations in the position of these sites relative to the position of the **promoter**, **activation** of the natural nac **promoter** or a nac **promoter** construct containing only a single high-affinity NRI approximately P binding site was strongly affected by subtle alterations in the position of the NRI approximately P binding site(s), indicating a face-of-the-helix dependency for activation.

L157 ANSWER 85 OF 225 HCAPLUS COPYRIGHT 2002 ACS
AB The upstream region of the isocitrate lyase gene (UPR-ICL, 1530bp) of an n-alkane-utilizable yeast, Candida tropicalis, induced gene expression in another yeast, Saccharomyces cerevisiae, when the yeasts were grown on acetate. Surprisingly, UPR-ICL displayed the same regulatory function n the bacterium Escherichia coli when grown on acetate. Surprisingly, UPR-ICL displayed the same regulatory function in the bacterium Escherichia coli when grown on acetate. The authors detd. the interesting nucleotide sequence of UPR-ICL. The deletion anal. of UPR-ICL in both cells revealed the presence of two distinct promoters: one was localized at -394 to -379 and regulated gene expression in S. cerevisiae; the other was located near the initiation codon and regulated gene expression in E. coli. The two promoter sequences were similar, but not identical to regulatory elements that have been previously reported in S. cerevisiae and E. coli, resp. Accordingly, the possibility of novel regulatory mechanisms could not be excluded. This is an interesting example of the presence of distinct cis-acting regulatory elements responsible for the induction of gene expression in one gene by acetate in both S. cerevisiae and E. coli. Preservation of such promoters through evolution is also discussed.

L157 ANSWER 94 OF 225 BIOTECHDS COPYRIGHT 2002 THOMSON DERWENT AND ISI
AB A stoichiometric limitation resulting from the phosphotransferase system, which greatly reduces the yield of aromatic metabolites (e.g. tryptophan, phenylalanine and tyrosine) in Escherichia coli AB2847, was overcome by **overexpression** of a **phosphoenolpyruvate-synthase** (PEP-synthase, EC-2.7.9.2) **gene** in the presence of glucose, using a plasmid pAT1 vector with a pps gene. The final concentration and yield (90% molar yield) of 3-deoxy-d-arabinoheptulosonic acid 7-phosphate were increased by almost 2-fold, to a near theoretical maximum. The PEP-synthase effect was not observed without overproduced transketolase (EC-2.2.1.1), suggesting that erythrose 4-phosphate was the first limiting metabolite. This work demonstrates that metabolic engineering of central metabolism according to stoichiometric analysis can lead to improvements in both productivity and yield. (26 ref)

L157 ANSWER 96 OF 225 HCAPLUS COPYRIGHT 2002 ACS
AB The glnA gene of Rhodobacter sphaeroides encoding glutamine synthetase (GS) has been cloned and sequenced. Mol. anal. revealed that there is a glnB gene upstream of glnA, in a single glnBA operon. A putative **glnAp1**-type promoter sequence, a consensus ntrC gene product binding site and a consensus upstream activator sequence were detected upstream of the glnB gene. The deduced amino acid sequences of the GS and GlnB proteins of R. sphaeroides showed strong homol. with the same proteins from other Gram-neg. bacteria. The sequence of the glnA gene isolated from glutamine auxotroph Gln83 was also detd. The glnA83 mutation was shown to result in premature termination of GS synthesis and formation of a 17 kDa C-truncated GS which could be complemented by a 5'-truncated glnA gene which encodes a 30 kDa N-truncated GS. This phenomenon is characteristic for interallelic complementation.

L157 ANSWER 100 OF 225 MEDLINE DUPLICATE 56
AB We investigated the relationship between Escherichia coli flagellar

expression and the regulation of acetyl phosphate synthesis and degradation. Using cells either wild type for acetyl phosphate metabolism or defective for phosphotransacetylase or acetate kinase, or both, we measured flagellar expression and the intracellular concentration of acetyl phosphate relative to growth phase and temperature. Under the conditions tested, we found that elevated levels of acetyl phosphate corresponded to inhibition of flagellar synthesis. To extend these observations, we measured the intracellular concentration of acetyl-CoA, the level of expression from the pta and ackA promoters, and the activities of phosphotransacetylase and acetate kinase derived from cell lysates. Relative to increasing culture density, acetyl-CoA levels and expression from both the pta and ackA promoters decreased. Relative to increasing temperature, expression from the ackA promoter decreased and phosphotransacetylase activity increased. In contrast, temperature had little or no effect on either **acetate** kinase activity or expression from the pta **promoter**. We propose that cells **regulate** intracellular **acetyl phosphate** concentrations relative to growth phase and temperature by **modulating** the availability of acetyl-CoA, the expression of ackA, and the activity of phosphotransacetylase.

L157 ANSWER 102 OF 225 MEDLINE DUPLICATE 58

AB In order to confirm functionally that a 208 bp fragment of the 5'-flanking sequence of the acuD gene of Aspergillus nidulans is the region responsible for **acetate inducibility** and catabolite repression, a hybrid **promoter** was constructed by insertion of this fragment into the promoter of the (highly expressed) oliC gene of A. nidulans. Analysis of expression of the lacZ reporter gene fused to the oliC/acuD **promoter** showed **induction** by **acetate** at much higher levels than wild-type acuD expression. **Acetate inducibility** of the hybrid **promoter** was dependent on the facB gene, demonstrating that a facB-dependent upstream activating sequence (UAS) for acetate must be located in the 208 bp acuD fragment. In parallel, partial relief of the transcriptional repression of acetate inducibility by sucrose and glucose was observed in a creA- background, showing that the 208 bp acuD fragment also responds to the creA gene. In addition, the results show that combination of a regulatory element from a low-expression promoter (acuD) with a high-expression constitutive promoter (oliC) leads to amplification of the level of regulated expression.

L157 ANSWER 104 OF 225 MEDLINE DUPLICATE 59

AB Analysis of the **promoter** region of the **acetate-induced** isocitrate lyase gene (acuD) of Aspergillus nidulans is described. Transcription start sites were detected at positions -163, -170 and approximately -281 upstream of the ATG. Transcription analysis showed that the acuD gene is transcribed during growth on acetate but not on hexoses or glycerol. Expression of the acuD gene was studied under inducing and repressing conditions in cre+, creA, creB and creC mutant strains, showing that the creA(d)-1 mutation led to slight derepression of isocitrate lyase. Regulation of expression of the acuD gene was also studied using an in-frame fusion with the lacZ gene of Escherichia coli. Several deletions were made in order to identify the regions responsible for acetate induction and repression. A deletion of the -412 to -200 bp upstream region resulted in loss of all promoter activity and a smaller deletion within this region abolished most of the acetate inducibility.

L157 ANSWER 110 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB The Bacillus subtilis gene encoding acetate kinase was identified on the basis of sequence similarity to the Escherichia coli ackA gene and to a second E. coli gene closely related to ackA. Insertional inactivation of this region of the B. subtilis chromosome resulted in the disappearance of acetate kinase enzyme activity in cell exts. The ackA gene was mapped to a site close to the ccpA gene, at 263.degree.. The transcriptional start

site for B. subtilis ackA was located 90 bp upstream from the start of the coding region, and expression was increased by growth in the presence of excess glucose. Growth of the AckA- mutant was inhibited by glucose, suggesting that acetate kinase is important for excretion of excess carbohydrate. The stimulation of ackA expression by glucose was blocked in a CcpA- mutant, indicating that CcpA, which is required for glucose repression of certain carbon source utilization genes, including amyE, may also be involved in activation of carbon excretion pathways. Two sequences resembling the amyO operator site were identified upstream of the ackA promoter; removal of this region resulted in loss of glucose activation of ackA expression.

L157 ANSWER 111 OF 225 HCAPLUS COPYRIGHT 2002 ACS
AB Transcription of many nitrogen-regulated (Ntr) genes requires the phosphorylated form of nitrogen regulator I (NRI, or NtrC), which binds to sites that are analogous to eukaryotic enhancers. A highly conserved regulatory domain contains the site of phosphorylation and controls the function of NRI. The authors analyzed the effects of substitutions in highly conserved residues that are part of the active site of phosphorylation of NRI in Escherichia coli. Fourteen substitutions of aspartate 54, the site of phosphorylation, impaired the response to nitrogen deprivation. Only one of these variants, NRI D-54 .fwdarw. E (NRI-D54E), could significantly stimulate transcription from **glnAp2**, the major promoter of the glnALG operon. Cells with this variant grew with arginine as a nitrogen source. Expts. with purified components showed that unphosphorylated NR1-D54E stimulated transcription. In contrast, substitutions at aspartate 11 were not as deleterious as those at aspartate 54. Finally, NR1-K103R, in which arginine replaces the absolutely conserved lysine, was shown to be functionally active and efficiently phosphorylated. This substitution appears to stabilize the phosphoaspartate of NRI. The differences between these results and those found for homologous proteins suggest that there may be significant differences in the way highly conserved residues participate in the transition to the activated state.

L157 ANSWER 112 OF 225 MEDLINE DUPLICATE 64
AB The functional organization of the glnB-A cluster of Azospirillum brasilense, which codes for the PII protein and glutamine synthetase, respectively, was studied with the aid of lacZ fusions, deletion mapping, site-directed mutagenesis, and complementation. It was shown previously by mRNA mapping that the cluster contains two tandemly organized promoters, glnBp1 and glnBp2, of the sigma 70 and sigma 54 types, respectively, upstream of glnB and a third unidentified promoter upstream of glnA. Data obtained with lacZ fusions in the wild-type strain confirmed that cotranscription of glnBA and transcription of glnA alone were oppositely **regulated** by the cell N status. Quantification of **promoter** activities showed a high level of transcription from glnBp1p2 and a low level from **glnAp** under conditions of nitrogen limitation. The opposite situation prevails under conditions of nitrogen excess. As a consequence, PII polypeptide synthesis is increased under conditions of nitrogen fixation, which strongly suggests that PII plays an important role under these conditions. Null mutant strains of glnB, ntrB-ntrC, nifA, and point mutant strains in glnA were analyzed. NtrB and NtrC are not involved in the regulation of glnBA expression, in contrast to PII and glutamine synthetase. Glutamine synthetase probably acts by modulating the intracellular N status, and PII acts by modifying the properties of an unidentified regulator which might be a functional homolog of NtrC. In addition, a Nif- null mutant strain of glnB was characterized further. A Nif+ phenotype was restored to the strain by nifA from Klebsiella pneumoniae but not by nifA from A. brasilense. This mutant strain is not impaired in NifA synthesis, which is relatively independent of the growth conditions in A. brasilense. (ABSTRACT TRUNCATED AT 250 WORDS)

L157 ANSWER 117 OF 225 MEDLINE DUPLICATE 68

AB Escherichia coli cells carrying the gltX351 allele are unable to grow at 42 degrees C (Ts phenotype) due to an altered glutamyl-tRNA synthetase. We found that gltX351 cells display a new phenotype termed Gsd-, i.e. an inability to raise glutamine synthetase activity above low constitutive levels in minimal medium with 6.8 mM glutamine as sole nitrogen source. When 0.5 mM NH4+ or 12 mM glutamate replaced glutamine, the glutamine synthetase activities of gltX351 cells were raised to wild-type levels. Northern experiments showed that the Gsd- phenotype is the result of an impairment in transcription initiation from the Ntr-**regulated promoter**, **glnAp2**. Intragenic and extragenic secondary mutations appeared frequently in gltX351 cells, which suppressed their Gsd- but not their Ts phenotype. Moreover, in heterozygous gltX+/gltX351 partial diploids, gltX351 was dominant for the Gsd- phenotype and recessive for the Tr phenotype. A slight increase in the glutamine pool and in the intracellular glutamine: 2-oxoglutarate ratio was also observed but this could not account for the Gsd- phenotype of gltX351 cells. In cells carrying gltX351 and a suppressor of the Gsd- phenotype, sup-1, tightly linked to gltX351, the glutamine pool and glutamine: 2-oxoglutarate intracellular ratio were even higher than in the gltX351 single mutant. These results indicate that the gltX351 mutant polypeptide may be the direct cause of the Gsd- phenotype. The possibility that it interacts with one or more components that trigger the Ntr response is discussed.

L157 ANSWER 119 OF 225 MEDLINE DUPLICATE 70

AB Phosphorylated nitrogen regulator I (NRI, also called NTRC), encoded by glnG (ntrC), stimulates transcription in Escherichia coli and other enteric bacteria from sites analogous to eukaryotic enhancers. We isolated 30 mutants, obtained without phenotypic selection, that have either a small insertion or deletion within glnG. Mutants were classified by the ability of NRI to repress the **glnAp1** and glnL **promoters** and to **activate** two versions of the nitrogen-**regulated glnAp2 promoter**; each activity was measured in cells grown with three concentrations of NRI. The results were interpreted within the framework of the three-domain hypothesis of NRI structure. NRI is thought to contain a phosphorylated regulatory domain that controls binding of ATP, a central domain that hydrolyzes ATP and interacts with RNA polymerase, and a DNA-binding region of unknown extent. Our results suggest that the 70 amino acids from residue 400 to the carboxyl terminus constitute a DNA-binding domain that includes residues for specific contacts and dimerization. Our results also suggest that (i) transcription from **glnAp2** without specific NRI-binding sites requires binding to sites with some similarity to the specific sites, and (ii) if an NRI variant can stimulate transcription, then increasing the concentration of NRI diminishes glnA expression for all mutants but one.

L157 ANSWER 126 OF 225 MEDLINE DUPLICATE 72

AB Fifteen-fold overexpression of phosphoenolpyruvate synthase (Pps) (EC 2.7.9.2) in Escherichia coli stimulated oxygen consumption in glucose minimal medium. A further increase in Pps overexpression to 30-fold stimulated glucose consumption by approximately 2-fold and resulted in an increased excretion of pyruvate and **acetate**. Insertion of two codons at the PvuII site in the **pps gene** abolished the enzymatic activity and eliminated the above-described effects. Both the active and the inactive proteins were detected at the predicted molecular weight by polyacrylamide gel electrophoresis. Therefore, the observed physiological changes were due to the activity of Pps. The higher specific rates of consumption of oxygen and glucose indicate a potential futile cycle between phosphoenolpyruvate (PEP) and pyruvate. A model for the stimulation of glucose uptake is presented; it involves an increased PEP/pyruvate ratio caused by the overexpressed Pps activity, leading to a stimulation of the PEP:sugar phosphotransferase system.

L157 ANSWER 127 OF 225 MEDLINE DUPLICATE 73

AB Transcription of the Ntr regulon is controlled by the two-component system consisting of the response regulator NRI (NtrC) and the kinase/phosphatase NRII (NtrB), which both phosphorylates and dephosphorylates NRI. Even though in vitro transcription from nitrogen-**regulated promoters** requires phosphorylated NRI, NRII-independent **activation** of NRI also occurs in vivo. We show here that this activation likely involves **acetyl phosphate**; it is eliminated by mutations that reduce synthesis of **acetyl phosphate** and is elevated by a mutation expected to cause accumulation of **acetyl phosphate**. With purified components, we investigated the mechanism by which **acetyl phosphate** stimulates glutamine synthetase synthesis. **Acetyl phosphate**, carbamyl phosphate, and phosphoramidate but not ATP or phosphoenolpyruvate acted as substrates for the autophosphorylation of NRI in vitro. Phosphorylated NRI produced by this mechanism exhibited the properties associated with NRI phosphorylated by NRII, including the activated ATPase activity of the central domain of NRI and the ability to **activate** transcription from the nitrogen-**regulated** glutamine synthetase **glnAp2 promoter**

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L157 ANSWER 128 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB The effect of phosphorylation of nitrogen regulator I (NRI) on its binding properties was studied. Both phosphorylated and unphosphorylated NRI bind linearly to a single binding site but cooperatively to two adjacent binding sites. Cooperative binding of NRI is severely affected by phosphorylation: half-maximal binding of NRI-phosphate is at 20-fold lower concns. than that of unphosphorylated NRI. This is more due to a huge increase in the cooperativity const.-which is the strength of interaction between two NRI dimers-than to an increase in the microscopic binding const. which is the binding affinity to a single binding site. In vitro transcription and DNA footprinting expts. showed that occupation of a single binding site by NRI is not enough for efficient activation and that activation only occurs at a higher NRI concn. An activation mechanism for NRI is proposed in which the phosphorylation of NRI induces a conformational change in the N-terminal domains of the NRI-phosphate dimers, which now interact strongly with each other, leading to a tetramerization of NRI upon binding to two adjacent binding sites. It is proposed that rather than the phosphorylation of NRI itself, the tetramerization of NRI-phosphate on DNA binding induces the conformational change of the central domain to the active conformation.

L157 ANSWER 131 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB Using freshly isolated maize mesophyll protoplasts and a transient expression method, the authors show that the transcriptional activity of seven maize photosynthetic gene promoters is specifically and coordinately repressed by the photosynthetic end-products sucrose and glucose, and by the exogenous carbon source acetate. Analyses of deleted, mutated, and hybrid **promoters** show that sugars and **acetate** inhibit the activity of distinct pos. upstream **regulatory** elements without a common consensus. The metabolic repression of photosynthetic genes overrides other forms of regulation by light, tissue type, and developmental stage, and appears to be a major regulatory circuit in higher plants.

L157 ANSWER 138 OF 225 MEDLINE DUPLICATE 78

AB Nitrogen regulator I (NRI [or NtrC])-phosphate stimulates transcription from the **glnAp2** promoter of the glnALG operon in enteric bacteria. Unlike most activators, NRI-phosphate can stimulate transcription without apparent activator binding sites. We observed that when lacZ was controlled by a minimal **glnAp2** promoter (without NRI binding sites) in Escherichia coli, lacZ expression was regulated by two different stimuli, the nitrogen status of the medium and the particular amino acid used as a nitrogen source. The latter stimulus did

not affect the activity of the wild-type **glnAp2** promoter, which has two high-affinity NRI binding sites. We present several lines of evidence that suggest that the concentration of NRI-phosphate limits the activity of the minimal **glnAp2 promoter** in vivo. Our results also suggest that nitrogen **regulator** II-dependent phosphorylation of NRI cannot account for the proposed variations in the concentration of NRI-phosphate. Therefore, to account for the **regulation** of the minimal **glnAp2 promoter** by two environmental stimuli, we propose that at least two protein kinases phosphorylate NRI during nitrogen-limited growth. We isolated and characterized mutants in which NRI could not stimulate transcription from the minimal **glnAp2 promoter** but could **activate** transcription from the wild-type **glnAp2 promoter**. These mutants could not utilize arginine or proline as a nitrogen source, suggesting that degradation of some nitrogen sources may require transcription from promoters similar to the minimal **glnAp2** promoter.

L157 ANSWER 141 OF 225 MEDLINE DUPLICATE 81

AB A mutation, serine 170 to alanine, in the proposed ATP binding site of the activator protein NTRC prevents transcriptional **activation** at sigma 54-dependent **promoters** both in vivo and in vitro. The rate of phosphorylation of the mutant protein by NTRB and the stability of mutant NTRC-phosphate were similar to those of wild-type NTRC. The phosphorylated mutant protein shows only a slight decrease in affinity (around 2-fold) for tandem NTRC binding sites in the Klebsiella pneumoniae nifL promoter suggesting that the mutation primarily influences the positive control function of NTRC. Moreover the mutant protein is trans dominant to the wild-type protein with respect to transcriptional **activation** at both the **glnAp2** and nifL **promoters** . In vitro footprinting experiments reveal that the mutant protein is unable to catalyse isomerisation of closed promoter complexes between sigma 54-RNA polymerase and the nifL promoter to open promoter complexes. However, the mutant protein retains the ability to increase the occupancy of the -24, -12 region by sigma 54-RNA polymerase, forming closed complexes at the nifL promoter, which are not detectable in the absence of NTRC. These data support a model in which the activator influences the formation of closed complexes at the nifL promoter in addition to its role in catalysing open complex formation.

L157 ANSWER 145 OF 225 MEDLINE DUPLICATE 85

AB Neurospora crassa acetyl CoA synthetase is highly induced when the growing mycelium is transferred from sucrose- to **acetate**-based medium. The **inducible promoter** of this gene has been isolated and used to control the expression of glutamate dehydrogenase. Transformants containing this expression cassette show gdh levels up to 25 times higher than the nontransformed host strain. This expression cassette will form the basis of a system of heterologous gene expression.

L157 ANSWER 146 OF 225 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L157 ANSWER 150 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB The protein nitrogen regulator I (NR1)-phosphate is known to activate the initiation of transcription of the E. coli glnA gene. This activation is facilitated by the binding of the protein to NR1-specific sites located upstream of the .sigma.54-dependent glnA promoter. To det. whether binding of NR1-phosphate to upstream sites is sufficient for **activation**, several **promoters** not normally **activated** by NR1-phosphate were placed downstream of NR1-binding sites, and activation in intact cells and in an in vitro transcription system was measured. .sigma.70-Dependent lac **promoter** was not **activated**. The .sigma.54-dependent Klebsiella pneumoniae nifH **promoter** was weakly **activated** and a nifH **promoter** altered in the RNA polymerase-binding site was almost as

well **activated** as the glnA **promoter**. Thus, the sensitivity of the susceptible promoter depends on the presence of NR1-binding sites, but that the presence of bound NR1-phosphate upstream of a **promoter** is not sufficient for **activation** of transcription by RNA polymerase. This activation is detd. by the structure of the RNA polymerase-binding site. The authors suggest that .sigma.54- but not .sigma.70-dependent **promoters** are susceptible to **activation** by NR1-phosphate and that the nucleotide sequence of the .sigma.54-RNA polymerase binding site is an important determinant of the efficiency of activation.

L157 ANSWER 154 OF 225 MEDLINE DUPLICATE 90

AB Mutations in the glnG gene of Escherichia coli that result in increased activity of nitrogen regulator I (NRI), the product of glnG, were obtained by two different selection procedures. The mutant proteins were purified and characterized. The concentrations of mutant proteins needed to **activate** transcription at the **glnAp2 promoter** were three to four times lower than that of the wild-type NRI. The rate of phosphorylation of these proteins and the stability of mutant NRI phosphate were found to be similar to those of the wild-type NRI. In one of the mutants, the site of the mutation was localized in the DNA region specifying the central domain of NRI.

L157 ANSWER 161 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB The role of the activator NRI-phosphate is to bring about the conversion of the closed .sigma.54-RNA polymerase **glnAp2** promoter complex to the open complex. The open complex which could be sepd. from unbound protein and small mols. by gel filtration, was found to contain NRI which was released during the initiation of transcription. The high affinity NRI-binding sites apparently facilitate open complex formation by increasing the NRI-phosphate concn. at the linked closed polymerase-promoter complex.

L157 ANSWER 163 OF 225 HCAPLUS COPYRIGHT 2002 ACS

AB In vivo footprints of the glnA regulatory region under activating conditions demonstrate that the 3 most upstream activator sequences bind the protein NRI in the cell. Together, protections at these sites span 6 of 7 consecutive major grooves and lie on the same helix face. E.sigma.54 protects 2 major grooves of DNA .apprxeq.60 base pairs downstream at the **glnAp2** promoter and primarily on the opposite helix face. Expts. using potassium permanganate to probe open complex formation in vivo demonstrate that NRI is absolutely required for E.sigma.54 to open the promoter DNA. Together, the di-Me sulfate and permanganate studies verify that E.sigma.54 occupies the **glnAp2** promoter in a closed complex in vivo even in the presence of excess nitrogen and the absence of NRI. Furthermore, the slow step in transcriptional activation is shown to be an NRI-dependent conformational change in the downstream promoter DNA, which results in DNA melting. These observations place interesting restrictions on models describing the mechanism by which NRI activates transcription from **glnAp2** at a distance.

L157 ANSWER 170 OF 225 MEDLINE DUPLICATE 98

AB The initiation of transcription from the nitrogen-**regulated promoter glnAp2** requires RNA polymerase containing sigma 54, the transcriptional activator NRI, and the protein kinase NRII, responsible for the conversion of NRI to the active NRI-phosphate. NRI-phosphate does not increase the ability of sigma 54-containing RNA polymerase to bind to the promoter, but rather stimulates the conversion of an initial promoter:polymerase complex to the transcriptionally active open complex. The presence on the DNA template of high-affinity binding sites for NRI/NRI-phosphate, normally located 130 and 100 bp upstream of the site of transcription initiation, results in a 4- to 5-fold lowering of the concentration of NRI required for the formation of the open complex. These high-affinity NRI binding sites facilitate open complex

formation when they are moved to positions 700 bp further upstream or 950 bp downstream of **glnAp2** on linear DNA templates.

L157 ANSWER 174 OF 225 LIFESCI COPYRIGHT 2002 CSA DUPLICATE 101
AB Transcription from **glnAp2** requires a specific sigma factor, sigma super(60), and core RNA polymerase (E). E sigma super(60) contains all the information required for promoter recognition (K sub(B) similar to 10 super(8) M super(-1)) but only rarely forms the promoter-polymerase open complex (k sub(2) similar to 6 x 10 super(-5) sec super(-1)). Transcription from **glnAp2** is activated by two additional proteins, NR sub(I) and NR sub(II) (k sub(2) similar to 6 x 10 super(-2) sec super(-1)). NR sub(II) is an NR sub(I) kinase that converts NR sub(I) to NR sub(I)-phosphate; NR sub(I)-phosphate is responsible for the activitation of transcription, probably forming parts of an "activation complex"

L157 ANSWER 181 OF 225 MEDLINE DUPLICATE 105
AB Transcription from nitrogen-**regulated promoters**, such as **glnAp2**, requires the glnG gene product, NRI, as well as the rpoN(glnF) gene product, sigma60, and is regulated by the glnL gene product, NRII. We find that in a reaction mixture containing NRI, NRII, and ATP, NRII catalyzes the transfer of the gamma phosphate of ATP to NRI. This covalent modification of NRI occurs concurrently with the acquisition of the ability by the reaction mixture to activate transcription from **glnAp2**. In the presence of PII, the product of glnB, NRII catalyzes the removal of the phosphate from NRI-phosphate. This reaction occurs concurrently with the loss by the reaction mixture of the ability to activate transcription from **glnAp2**. On the basis of this evidence, we propose that NRI-phosphate **activates** transcription from nitrogen-**regulated promoters** and that the role of NRII is control of the formation and breakdown of NRI-phosphate in response to cellular signals of nitrogen availability.

L157 ANSWER 191 OF 225 MEDLINE DUPLICATE 112
AB We have shown that the purified glnF (ntrA) product of Escherichia coli binds to core RNA polymerase. Together these proteins initiated transcription at the nitrogen-**regulated promoter** **glnAp2** on a supercoiled template. The initiation of transcription at **glnAp2** on a linear template required in addition NRI, the product of glnG (ntrC), and NRII2302, the product of a mutant allele of glnL (ntrB). These results identify the glnF product as a new sigma factor specifically required for the transcription of nitrogen-**regulated** and of nitrogen-fixation **promoters**. We propose rpoN as the proper designation for glnF, and sigma 60 for its product. Our results indicate that sigma 60 RNA polymerase recognizes the nitrogen-**regulated**/nitrogen-fixation **promoter** consensus sequence C-T-G-G-Y-A-Y-R-N4-T-T-G-C-A. Initiation of transcription in the intact cell appears to require in addition the active form of NRI, the product of glnG. Conversion of NRI to its active form is apparently brought about by NRII, the product of glnL, in response to nitrogen deprivation.

L157 ANSWER 192 OF 225 MEDLINE DUPLICATE 113
AB We have determined that the glnA gene of the complex glnALG operon of Escherichia coli is transcribed from tandem promoters. Expression from the upstream **promoter**, **glnAp1**, requires the catabolite **activating** protein, is repressed by nitrogen regulator I (NRI), the product of glnG, and produces a transcript with an untranslated leader of 187 nucleotides. Expression from the downstream promoter, **glnAp2**, requires NRI as well as the glnF product; full expression also requires growth in a nitrogen-limited environment. The downstream transcript has an untranslated leader of 73 nucleotides. We also provide evidence that the function of the glnL product is to mediate the interconversion of NRI between a form capable of activating **glnAp2** and an inactive form in response to changes in the intracellular

concentration of ammonia. The function of the two minor promoters of the glnALG operon, **glnAp1** and glnLp, is to maintain the products of glnA, glutamine synthetase, an essential enzyme, and of glnG, NRI, an activator of nitrogen-controlled genes, during carbon-limited growth.

L157 ANSWER 203 OF 225 MEDLINE DUPLICATE 120
AB In enteric bacteria products of nitrogen regulatory genes ntrA, ntrB and ntrC are known to regulate transcription both positively and negatively at glnA, the structural gene encoding glutamine synthetase [L-glutamate:ammonia-ligase (ADP-forming), EC 6.3.1.2]. We have characterized two types of cis-acting mutations in the glnA **promoter-regulatory** region. One type, which we have called **promoter** Up [**glnAp** (Up)], elevates transcription of glnA to high levels without need for ntr-mediated activation but leaves expression sensitive to ntr-mediated repression. The other type renders glnA transcription insensitive to repression but leaves it normally responsive to **activation**. Properties of the two types of **promoter-regulatory** mutations suggest that sites for ntr-mediated **activation** of glnA transcription are functionally distinct from sites for ntr-mediated repression.

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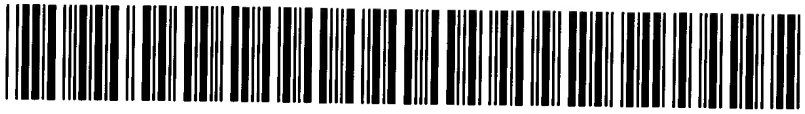

Creation date: 10-06-2003
Indexing Officer: JROMANI - JOHN ROMANI
Team: OIPEBackFileIndexing
Dossier: 09626612

Legal Date: 11-06-2002

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